SURGERY, GYNECOLOGY AND OBSTETRICS

AN INTERNATIONAL MAGAZINE, PUBLISHED MONTHLY

VOLUME 61 NOVEMBER, 1935 NUMBER 5

THE EXPERIMENTAL PRODUCTION OF CHOLESTEROSIS OF THE GALL BLADDER

WITH OBSERVATIONS ON THE CHOLESTEROL ABSORPTIVE PROPERTIES OF THE GALL-BLADDER WALL[1]

LOUIS M. ROUSSELOT, M.D., AND LOUIS BAUMAN, M.D., PH.D., NEW YORK, NEW YORK

THE appearance of lipoid deposits in the wall of the gall bladder early attracted the attention of pathological anatomists. Thus, Virchow in 1857 commented on the presence of lipoid material in the epithelium of many of the gall bladders obtained at necropsy. Naunyn, in his treatise on gall stones, states that he found an increased concentration of cholesterol in the gall bladder bile of gall stone cases. He believed this was due to secretory activity of the gall-bladder epithelium. Years later Aschoff presented the opposite concept, namely that cholesterol could be absorbed by the gall-bladder wall. Subsequently, many publications have appeared to support one or the other belief.

The similarity of the histological structure of the gall bladder and intestine, and their derivation from a common anlage lead many to speculate as to possible similar functions. Thus, Policard, Sweet, Halpert, and Mentzer (19) thought that the gall-bladder mucosa possessed absorptive properties. Sweet, in fact, believed that few, if any, of the bile constituents left the gall bladder by way of the cystic duct. After studying similar histological material, other observers have arrived at exactly the opposite conclusion, thus Chauffard, Gosset, and Lichtwitz believed that the gall-bladder mucosa exercised a secretory function as far as cholesterol was concerned.

Sir Berkeley Moynihan first drew attention to the clinical-pathological entity which was later named the "strawberry gall bladder" by MacCarthy, and more aptly cholesterosis of the gall bladder by Mentzer (19). Using microchemical reactions, differential stains, and the polarizing microscope, Policard (27), Boyd, and Illingworth concluded that the epithelial deposits of lipoid material in cholesterosis cases consisted principally of the ester of cholesterol, and that this followed absorption of cholesterol from the bile.

In spite of the many opinions, direct experimental proof of the cholesterol function of the gall bladder is meager. A review of the various approaches to the problem is of interest.

Aschoff, after ligating the cystic duct of dogs and injecting neutral fats and cholesterol dissolved in olive oil into the gall bladder, observed lipoid deposits in the epithelial cells and concluded that this was due to absorption. Apparently he failed to consider that the gall-bladder epithelium of normal dogs may show varying amounts of lipoid material, for Chauffard, in a series of 6 normal animals, found lipoid in 3, while Boyd (4) found it present in every one of 12 animals. In our own group of 7 controls, small to large deposits were demonstrable in 6.

Torinoumi, after injecting normal bile and bile fortified by the addition of cholesterol

[1]From the Departments of Surgery of the Presbyterian Hospital and the College of Physicians and Surgeons, Columbia University.

TABLE I.—THE CHANGE IN CHOLESTEROL CONTENT OF SOLUTIONS SUBJECTED TO GALL-BLADDER ACTIVITY

Dog No.	Cholesterol injected mgm.	Cholesterol recovered mgm.	Per cent loss	Length of time in gall bladder Hours
12167	36	14.2	60.5	24½
	36	12.4	66.1	24
12172	28	11.0	60.5	20½
	28	14.0	50.0	4¼
12199	28	27.7	.09	6
	28	25.9	7.5	18
12222	24	10.	58.3	19
	24	13.0	45.8	23
12252	28	34.3	+22.4	23½
	28	22.2	21.0	23¼
12289	60	60.0	0.0	24
	60	30.6	49.0	24
12301	32	32.0	0.0	25½
	32	0.0	100.0	22¼
12336	32	30.0	6.25	24
	32	29.5	7.8	24

TABLE II.—THE CHOLESTEROL CONTENT OF THE GALL-BLADDER WALL OF DOGS INJECTED WITH A SOLUTION OF CHOLESTEROL IN BILE SALT

Number	Free cholesterol Per cent*	Ester cholesterol Per cent*
12222	1.26	.97
12252	1.89	.47
12287	1.05	.49
12289	1.30	.35
12301	1.53	.84
12336	1.38	.87
Average	1.40	.66
Total cholesterol content		2.06

*The values are expressed in terms of dry gall-bladder substance.

into the gall bladder, reported absorption in 3 experiments, and secretion in 2 infected cases. He concluded that, while cholesterol is normally absorbed, the process may be reversed in the presence of infection.

Illingworth injected bile to which cholesterol ester was added (a substance rarely found in human bile—Pierce, 25) into the gall bladder of cats and found a loss of about 50 per cent. He reports only two experiments of this type.

Elman and Taussig, and Elman and Graham injected bile into the gall bladder of the dog with the cystic duct ligated. They found an increase in the cholesterol content after a period of from 2 to 16 days. In these experiments, the partitioning ligature method of Rous and McMaster was used. Samples of gall bladder and hepatic bile were analyzed. The cholesterol content of the gall-bladder fraction was higher than could be accounted for by concentration, hence they concluded that the gall bladder secreted cholesterol.

Blaisdell and Chandler, after producing hypercholesteremia in rabbits and dogs, found microscopic evidence of cholesterol in the epithelium and submucosa of the gall bladder. This occurred only when the cystic duct was patent and represented one of many foci that were present in various organs. The gall-bladder infiltration was explained on the basis of absorption.

Recently Patey, working along similar lines produced a hypercholesteremia in rabbits. After inducing inflammatory changes in the gall-bladder wall, he was able to demonstrate microscopic deposits of lipoid in the gall-bladder mucosa in only 7 of 19 experiments. In contrast to the previous authors he interpreted the process as one of secretion.

Ravdin (28, 29) and his colleagues were unable to demonstrate absorption or secretion of cholesterol by the normal gall bladder of the dog. The experiments of Wilkie and Doubilet led them to conclude that normally cholesterol passes through the gall-bladder mucosa into the bile, but the process may be reversed depending on the relative concentration of the cholesterol in the blood and the gall-bladder bile. Dostal believed that the normal gall-bladder mucosa secreted cholesterol in negligible amounts.

Cholelithiasis and cholesterosis, and the frequent association of the two conditions is a problem that has interested us for some time. Mentzer (20, 21) at the Mayo Clinic, found stones in 60 per cent of the cases of cholesterosis in his surgical material and only 2.4 per cent in a study of necropsy specimens. In an examination of the surgical material of the Presbyterian Hospital, we have found a much higher incidence in that 75 per cent of the cases of cholesterosis also had gall stones. Because of this frequent association, a causal relationship between the two conditions has been suggested. Thus, Gosset (12), Boyd (3)

TABLE III.—THE CHOLESTEROL CONTENT OF THE GALL-BLADDER WALL OF NORMAL DOGS

Number	Free cholesterol Per cent	Ester cholesterol Per cent
1	.23	0
2	.12	0
3	.37	.21
4	.56	.06
5	0	.55
336	.97	.28
550	1.50	1.05
551	1.53	.64
Average	.66	.35
Total cholesterol content		1.01

and Elman (9) agreed that the later stage of cholesterosis may lead to gall-stone formation, though they disagreed as to the origin of the cholesterol found in the wall.

EXPERIMENTAL

An attempt to study the fate of cholesterol in the gall bladder was made along the following lines.

Method. Large healthy dogs were operated upon under ether anesthesia, and the biliary tract was exposed. Anomalous bile ducts were carefully sought for in the region of gall bladder and cystic duct and these were ligated if they entered either of these structures. The gall bladder was then catheterized after the method used by Ravdin (28). A soft No. 8 F rubber catheter was passed through a small incision in the common duct just below the cystic duct. The catheter was then continued up the cystic duct into the gall bladder. The central hepatic duct was ligated above the cystic and below the entrance of the catheter. This system did not leak, did not occlude the rich vascular and lymphatic drainage along the cystic duct, and allowed sufficient bile to enter the duodenum so as to interfere as little as possible with digestion. The gall bladder was then irrigated with normal saline until a clear return was obtained. Saline was then injected and the capacity of the viscus determined. The saline solution was left in about 5 hours. This allowed sufficient time for the animal to recover from the immediate effects of the anesthesia and gave us another clue as to the presence of accessory ducts not detected at operation. At the end of 5 hours the gall bladder was again irrigated with saline

TABLE IV.—THE CHOLESTEROL CONTENT OF THE GALL-BLADDER WALL OF DOGS INJECTED WITH SALINE SOLUTION

Number	Free cholesterol Per cent	Ester cholesterol Per cent
12320	.98	.66
12332	.85	.35
12368	1.13	.26
12386	1.10	.18
Average	1.01	.36
Total cholesterol content		1.37

TABLE V.—THE CHOLESTEROL CONTENT OF THE GALL-BLADDER WALL OF DOGS INJECTED WITH BILE SALT SOLUTION

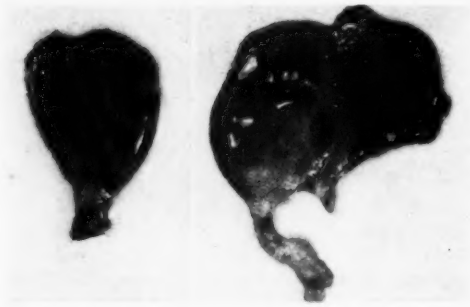
Number	Free cholesterol Per cent	Ester cholesterol Per cent
12420	1.07	0
12448	1.10	.36
Average	1.08	.18
Total cholesterol content		1.26

and the experimental solution instilled. After 24 hours, the gall-bladder contents were aspirated, the viscus irrigated with saline, and all the washings added to the sample. A second injection of the experimental solution was then made and again removed after a 24 hour stay in the gall bladder. Duplicate samples of the injection fluid were taken at each injection for check analyses of cholesterol by the Windhaus gravimetric method. The cholesterol solution contained 0.2 per cent of cholesterol dissolved in a 4 per cent solution of conjugated bile salts. This is the first time, we believe, that a true solution of this type was used rather than bile or a colloidal suspension of cholesterol.

DISCUSSION OF CHEMICAL FINDINGS

As was expected, there was a constant decrease in the volume of the injected fluid. In 5 of the animals an average loss of about 50 per cent in cholesterol took place (Table I). In 2 cases, 12,199 and 12,336, the loss was so small as to be within the realm of experimental error. Animal No. 12,252 showed a gain in the first 24 hours and a loss in the second 24 hours.

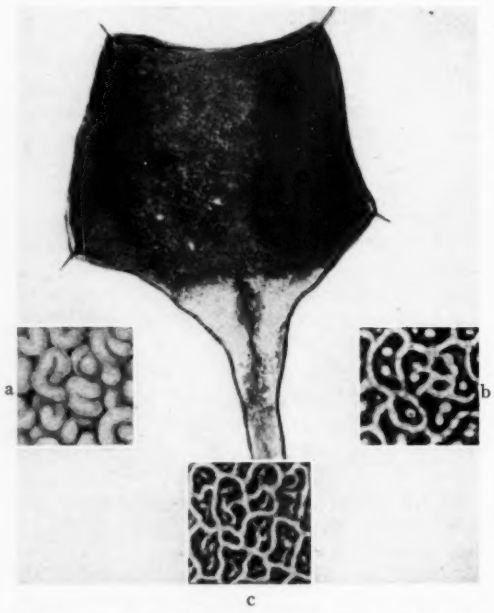
After the last sample of fluid was obtained the animal was immediately sacrificed and an autopsy was performed. The gall bladder was then removed, sections taken from the am-



a b

Fig. 1a. Photograph of normal gall bladder of the dog (actual size). b, Photograph of gall bladder of experimental animal. Note white opaque swollen villi in ampullary region. These changes are less marked toward the fundus.

Fig. 2. Same as Figure 1a, only enlarged one and two-third times. Area from ampulla shown. The heavily laden lipoid containing villi stand out prominently.



a b c

Fig. 3. Drawing illustrating marked gross changes in the region of the ampulla and cystic duct. A less intense change is seen toward the fundus. a, Appearance of white opaque lipoid laden villi in the ampullary region as seen with a magnifying glass. The intervening crypts are almost obliterated. b, Section from the margins of Figure 3 showing almost normal appearing translucent villi with deep intervening crypts. (Same magnification as Figure 3a.) Drawing by A. Feinberg. c, Appearance of villi in the light colored area in the fundus. The change is less marked. (Same magnification as Figure 3a.)

pulla and fundus and the remainder was used for quantitative determination of cholesterol and cholesterol ester. Comparable analyses were also done (1) on the gall bladders of normal dogs (2) on dogs that were subjected to the same operative procedure but in which only saline solution was injected, and a third group that were injected with bile salt solution alone.

In the walls of human "strawberry" gall bladders we have consistently found an increase in the cholesterol and particularly in cholesterol ester as compared with normal gall bladders or those the seat of cholecystitis. In the animals injected with cholesterol solution, the average total cholesterol content was 2.06 per cent (Table II); as compared with 1.01 per cent (Table III) in normal untreated dogs; 1.37 per cent (Table IV) in the saline controls; and 1.26 per cent (Table V) in the bile salt controls.

It is interesting to note the increment in the cholesterol ester content of our experimental animals as compared with the normal and the controls. If we take the average cholesterol ester content of the three control series as 0.3 per cent, the increase in the cholesterol ester of the injected animals was 100 per cent (0.66 per cent), this we think is far more than could reasonably be expected from any slight exudation of cholesterol rich serum due to an inflammatory reaction. Wells (34) has shown

that inflammatory exudates are rich in cholesterol.

The cholesterol and cholesterol esters in the wall of the gall bladder was determined by adaptation of the methods proposed by Fex, and Gardner and Gainesborough as follows:— A small amount of gall bladder was dried to constant weight at 110 degrees to determine the solid matter. The remainder was dissolved in 2 per cent sodium hydroxide by heating for 3 or 4 hours on the water bath. The alkaline solution was exhaustively extracted with ether. The residue which remained after evaporation of the ether was taken up in alcohol and free cholesterol precipitated with digitonin and weighed. The filtrate containing the cholesterol esters was saponified with 4 per cent sodium ethylate for 8 hours, then extracted and the cholesterol determined as above.

DISCUSSION OF PATHOLOGICAL FINDINGS

The gall bladder into which the cholesterol solutions had been injected showed a constant gross pathological change which was not observed in any of the controls. The villi of the mucosa appeared swollen, yellowish-white, and opaque in contrast to the thin greenish translucent villi of the normal organ (Figs. 1 and 2). This change was constantly present in the region of the ampulla but a patchy distribution and a diffuse process was observed in several cases (Fig. 3). In some instances the villi were so broad that they encroached on one another and the intervening crypts were difficult to see (Fig. 3a). These changes were best seen with a hand lens and are well illustrated in Figures 2 and 3a and 3b. The lesions produced in these experimental animals is strikingly similar to the illustrations presented by Whipple in his clinical article on lipoid gall bladder.

The histological preparations were taken from the ampulla and fundus, and stained with hematoxylin-eosin and Scharlach R. In some cases, unstained sections were studied with the polarizing microscope. The experimental animals all showed the brilliant red deposits of lipoid in the epithelial cells, and occasionally in the stroma. Anisotropic lipoid was also present in these same cells. Although heavy deposits of visible lipoid occurred in all our experimental animals, we placed little significance on these findings, inasmuch as 6 of 7 of our normal unoperated upon controls showed varying amounts of microscopically visible lipoid. In all our experimental animals the sections showed mild inflammatory changes in the submucosa. We agree with Illingworth that all the cholesterol in the gall-bladder wall may not be demonstrable by staining methods. (Free cholesterol itself does not take the fat stain.) He felt that cholesterol may be bound up with other lipoids in such a manner as to render it unrecognizable by staining reactions or physical properties and that its passage through the gall bladder wall may likewise be obscured.

SUMMARY

When solutions of cholesterol in the concentrations mentioned are placed in the gall bladder of a dog, there is a consistent loss of the lipoid averaging about 50 per cent in 24 hours.

A gross pathological lesion was produced in every experiment that closely resembled the human picture of cholesterosis.

An increment in the cholesterol ester content of the gall-bladder wall was obtained. This is consistent with findings in the human specimens.

No apparent increase in the free cholesterol content of the gall-bladder wall could be demonstrated.

This evidence, under the conditions previously outlined, suggests the absorption of cholesterol by the gall-bladder mucosa.

We wish to express our indebtedness to Dr. A. P. Stout for his kind assistance in the study of the pathological material. Acknowledgment is also made of the technical assistance of Margaret Hamlin, M.A., and Albrecht Sauerman, Ph.D.

BIBLIOGRAPHY

1. Aschoff, L. Muenchen. med. Wchnschr., 1906, 53: 1847.
2. Blaisdell, F. E., and Chandler, L. R. Am. J. M. Sc., 1927, 174: 492.
3. Boyd, William. Brit. J. Surg., 1922, 10: 337.
4. Idem. Canadian M. Ass. J., 1922, 12: 689.
5. Chauffard, A., Laroche, G., and Grigaut, A. Compt. rend. Soc. de biol., 1913, 74: 1005.
6. Dostal, Hrdina, and Goff. Proc. Soc. Exper. Biol. & Med., 1932, 29: 541.
7. Elman, R., and Graham E. Arch. Surg., 1932, 24: 14.

8. ELMAN, R., and TAUSSIG, J. B. Proc. Soc. Exper. Biol. & Med., 1931, 28: 1066, 1068, 1070.
9. Idem. J. Exper. Med., 1931, 54: 775.
10. FEX, J. Biochem. Ztschr., 1920, 104, 82.
11. GARDNER, J. A., and GAINESBOROUGH H. Biochem. J., 1927, 21: 130.
12. GOSSET, M., LOEWY, G., and MAGROU, J. Compt. rend. Soc. de biol., 1920, 83: 1207.
13. Idem. Bull. et mém. Soc. de Par., 1921, 47: 1391.
14. HALPERT, B. Med. Klin., 1924, No. 13, 408.
15. Ibid. No. 52.
16. ILLINGWORTH, C. F. W. Brit. J. Surg., 1929, 17: 203.
17. LICHTWITZ, L. Ergebn. d. inn. Med. u. Kinderh., 1922, 13: 56.
18. MACCARTHY, W. C. Ann. Surg., 1910, 51: 651.
19. MENTZER, S. H. Am. J. Path., 1925, 1: 383.
20. Idem. Surg., Gynec. & Obst., 1926, 42: 782.
21. Idem. J. Am. M. Ass., 1928, 90: 607.
22. MOYNIHAN, B. G. A. Ann. Surg., 1909, 50: 1265.
23. NAUNYN, B. A Treatise on Cholelithiasis. New Sydenham Society, 1st English ed., 1896.
24. PATEY, D. H. Brit. J. Surg., 1934, 22: 378.
25. PIERCE, S. J. S. Arch. f. klin. Med., 1912, 106: 337.
26. POLICARD, A. Compt. rend. Soc. de biol., 1914, 76: 338.
27. Ibid. 518.
28. RAVDIN, JOHNSTON, et al. Am. J. Physiol., 1932, 99: 638.
29. RIEGAL, JOHNSTON, and RAVDIN. J. Exper. Med., 1932, 56: 1.
30. ROUS, P., and MCMASTER, P. D. J. Exper. Med., 1921, 34: 47.
31. SWEET, J. Internat. Clin., 1924, 1: 187.
32. TORINOUMI, K. Beitr. z. path. Anat. u. z. allg. Path., 1924, 72: 456.
33. VIRCHOW, R. Arch. f. path. Anat., 1857, 11: 574.
34. WELLS, H. G. Chemical Pathology, 5th ed., pp. 300, 399. Philadelphia: W. B. Saunders Co., 1925.
35. WHIPPLE, A. O. Nelson Loose-Leaf Living Surgery, Vol. 5, p. 460.
36. WILKIE, A., and DOUBILET. Arch. Surg., 1933, 26: 110.

THE INTERVERTEBRAL DISC

Embryology, Anatomy, Physiology, and Pathology[1]

ROBERT J. JOPLIN, A.B., M.D., Boston, Massachusetts
Assistant in the Department of Orthopedic Surgery of the Harvard Medical School
From the Orthopedic and Pathological Departments of the Children's Hospital, Boston

In attempting to analyze the etiological factors which make up the clinical orthopedic problem of this day and age, the spine plays a major rôle. Schmorl is responsible for making popular a particular portion of the vertebral column which previously had been allowed to go by almost unrecognized. Instead of the main supporting structure of our head and trunk being regarded simply as a column of blocks separated by little fibrocartilaginous discs, an analysis of the component parts of each block and disc has changed our semi-flexible column into a very complex structure subject to a wide range of changes with far reaching results.

As a skeletal organ, the spine is unique in structure and function. The joints differ from other joints of the body, as pointed out by Beadle, because not only do they possess flexion and rotation, but their broad surfaces bear the greater part of the burden of the spine and upon them fall the various stresses and strains of functional activity as well as the physical shocks leading to mechanical injury. The maximum effect is upon the structures between the bodies of the vertebræ. Instead of the usual joint cavity, there is a highly elastic and fluid tissue mass, the nucleus pulposus, a clear understanding of which requires a review of the embryological development.

EMBRYOLOGY

Von Luschka, in 1858, was the first to report changes in the notochord leading to the formation of the intervertebral disc; Keys and Compere have summarized the more recent findings. In the human embryo, slightly over 2 millimeters long, a ridge of entodermal cells appears in the mid-sagittal plane and later separates as the notochord, in turn, is surrounded by mesenchymal cells from the sclerotomes.

The aorta then sends in parallel branches which divide these cells into groups or segments (Fig. 1). The cells which are nearest the blood vessels appear to receive more nourishment and differentiate more rapidly; that is, those just above the artery and those just below, rapidly grow to form the primordia, or genesis, of the vertebral bodies. Whereas, the cells farther away from the blood vessels remain relatively unchanged as the primordia of the intervertebral discs.

In a mid-sagittal section at this stage, the notochord appears as a tube passing through segmented masses of cells. In the lighter segment, where the cells have grown by adding more cytoplasm, the notochord appears to be compressed in such a way that its cells are beginning to be extruded above and below toward the intervertebral spaces (Fig. 2). Finally only a mucoid streak remains through the vertebral bodies. Still later, the cells of the intervertebral region differentiate into an elongated fibroblastic type, arrange themselves along a vertical axis, and become attached above and below to the vertebral bodies.

In a 10 weeks old embryo, which is approximately 5 centimeters in length, the vertebral bodies are cartilaginous and possess ossification centers. The notochord material may henceforth be regarded as the nucleus pulposus and its surrounding fibrocartilage envelope as the annulus fibrosus or annulus lamellosus. As the age of the embryo advances, the mucoid content of the nucleus pulposus is increased.

ANATOMY

A cross section of an intervertebral disc from an infant 5 months of age reveals a gradual change from the hyaline cartilage type of cell at the periphery to an almost complete disappearance of cellular structure within the interior. First, there is the gradual loss of chondromucoid substance which leaves iso-

[1]Read at the Children's Hospital, Boston, October 19, 1934, as a part of the clinical program of the orthopedic section of the American College of Surgeons.

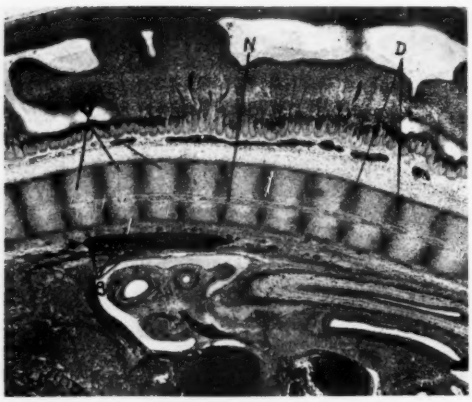


Fig. 1 (2d to 9th thoracic vertebral region in an embryo 14.1 millimeters long, 6 weeks old). The notochord, *N*, is seen passing through the segmented masses of cells. Above is dorsal, below is ventral where cross sectioned blood vessels, *B*, may be seen opposite the lighter areas, *V*, which form the vertebral bodies; the darker areas, *D*, form the discs.

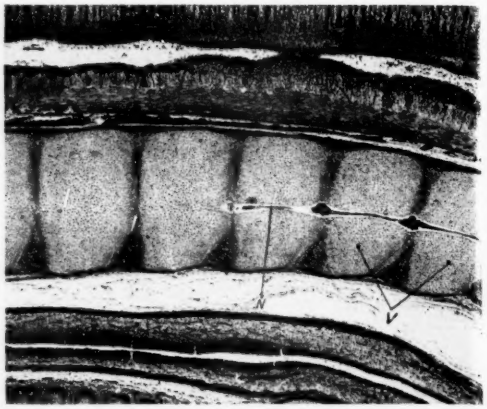


Fig. 2 (5th to 8th cervical region in an embryo 31 millimeters long, 8 weeks old). The notochord, *N*, is narrower in the vertebral body regions *V*, but more globular between.

lated cartilage cells in their lacunæ. Farther toward the interior, the lacunar membrane is present but the cells become pycnotic and finally disappear entirely, leaving only a fibrillar network. In the central portion of the disc, a small clump of cells may be found (Fig. 3) but they appear a little denser and resemble prechondral tissue; these are the last remaining notochord cells. The mucoid content of the nucleus pulposus is markedly increased as the infant gets older. It becomes increasingly difficult to identify notochord cells with the advance in age, though remnants of these cells have been reported in the adult. About the time the child starts to walk the growth of the disc is chiefly by proliferation of the fibrous element.

The adult disc shows microscopically a very loose and translucent network of fine fibrous strands which run an irregular, wavy course. In the meshes lie a profusion of long connective tissue cells and numerous cartilage cells.

Fig. 3. High power photomicrograph of a section of the intervertebral disc from an infant 5 months old showing the web-like fibrillar network, *F*, a few scattered cartilage cells, *C*, and a small clump of what appear to be the last remnants of the notochord cells *N*.

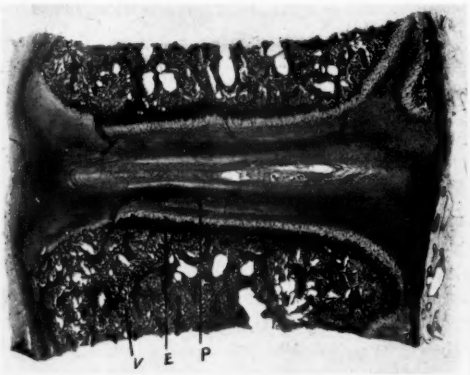


Fig. 4. Photomicrograph of a sagitally cut section showing two bony vertebral bodies, *V*, enchondral bone formation, *E*, and the cartilaginous plates, *P*, which overlap somewhat anteriorly.

A cross section of an 8 months old infant's spine reveals by gross examination, the enchondral bone formation which proceeds from the center of the vertebra toward the cartilaginous plates, between which lies the disc (Fig. 4). At the periphery, the cartilage plate overlaps the anterior and lateral borders of the osseous vertebra and forms an incomplete bony ring, the so-called "epiphyseal ring," which Schmorl calls the "rim ledge." Enchondral bone formation ceases and fusion between the rim ledge and body of the vertebra occur simultaneously when full growth is reached.

On the adult vertebral body (Fig. 5) the rim ledge measures about 2 to 3 millimeters in width and stands 1.5 to 2 millimeters in height above the surface of the vertebra as a firm, compact, smooth, bony ring which partly encloses the disc anteriorly and laterally but not posteriorly. Into this compact bone the annulus fibrosus fibers are firmly attached as Sharpey fibers. The remaining central surface of the vertebra is composed of a perforated plate which is merely the bare exposed end of spongy bone which impinges immediately on the cartilaginous plate of the intervertebral disc. It may be mentioned here that these perforations may be enlarged or easily broken through by protrusions of disc tissue.

The intervertebral disc when fully developed is a most complex and highly specialized organ. It consists of three parts: the cartilaginous plates enclosing it above and below, next the surrounding annulus lamellosus which encloses the innermost structure, the nucleus pulposus.

Fig. 6. Photograph of a mid-sagittal section of the vertebral column of a 4 weeks old infant; no fixation has been used. The nuclei pulposi, *N*, can be seen extruded clearly above the surfaces of the vertebral bodies.

The blood supply of the intervertebral disc is not clearly understood. Bohmig and Ubermuth are reported to have demonstrated in embryos that 3 vessels enter the intervertebral disc from above and 3 from below; these vessels retrogress during the course of life until, at the end of growth, the intervertebral disc is completely without vessels.

PHYSIOLOGY

It is the nucleus pulposus which plays the most outstanding rôle in the pathological changes which are to be described. When the spine of a young person (Fig. 6) especially of a child, is sawed through in a sagittal plane, the nucleus swells strongly forward as a white, translucent cushion which must have been under considerable pressure.

In position, the nucleus pulposus is situated always rather more posteriorly than centrally.

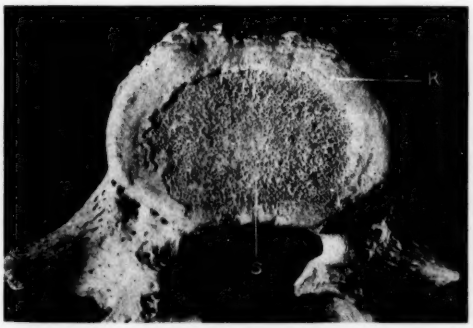


Fig. 5. Photograph of an old macerated vertebra which shows a normal center with the rim ledge, *R*, complete on the front and lateral sides but deficient posteriorly; the mid-portion of the picture reveals the perforated plate of spongy bone, *S*.

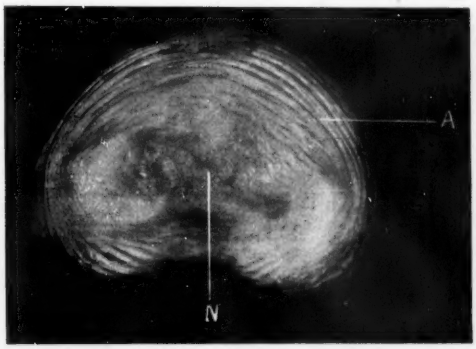


Fig. 7. Photograph of a normal disc removed at autopsy from a woman 30 years old. The horizontally cut section shows the annulus fibers, *A*, clearly as strong bands; the more homogeneous central portion contains the gelatinous nucleus pulposus, *N*.

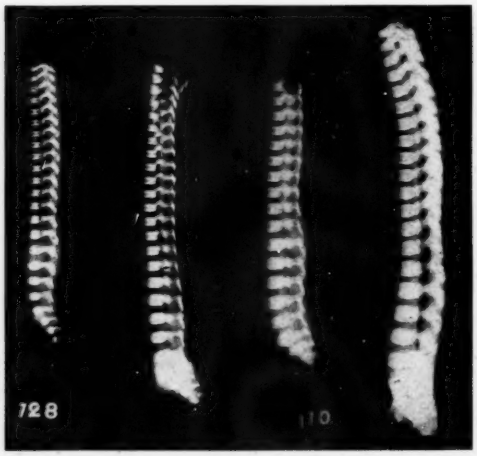


Fig. 8. Lateral roentgenograms of 4 spinal columns. The one on the extreme left is from a 7 months old embryo which has discs almost as high as the vertebral bodies. The second is from an infant 1 week old; the third is from an infant 3 weeks old; and the last is from an infant of 3 months. The discs appear relatively lower as the age increases. The notches in the anterior edges of the vertebral bodies are for the entrance of blood vessels.

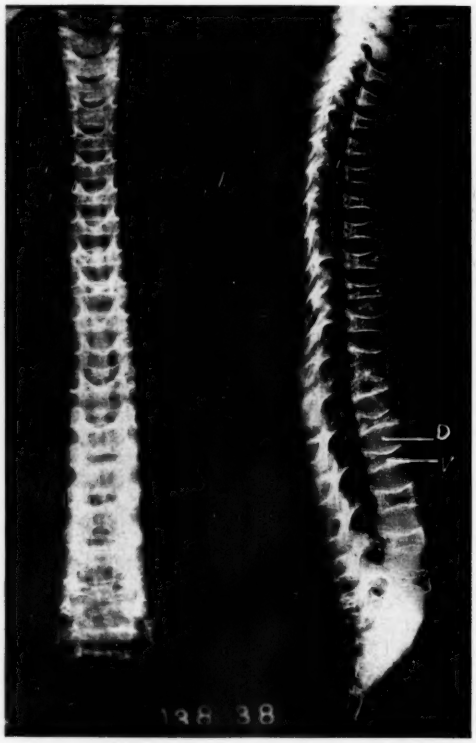


Fig. 9. Anteroposterior and lateral roentgenograms of a spinal column of a girl 3½ years old who died of a primary liver tumor producing marked osteoporosis. Here the discs, *D*, are much thicker than the vertebral bodies, *V*.

This varies in different spinal segments; it is farther forward in the upper dorsal region.

There is no definite line of demarkation separating the nucleus pulposus from the annulus fibrosus though on horizontal section the two may be clearly distinguished. The annulus, of course, gives the permanent form and size to the disc as well as being the part where most of the strength and tenacity has its seat. Toward the periphery, its concentric folds stand out as stout glistening bands which encircle the whole disc surface (Fig. 7). The number of these folds vary; in the lumbar spine there are 10 to 12 exceedingly stout ones; in the lower dorsal region, only 6 lamellæ may be counted. It is important to note that not only is there a lack of support from the bony rim ledge posteriorly, but the concentric folds of fibrous tissue also are fewer and thinner here where they are attached to the posterior longitudinal spinal ligament: this ligament is a much weaker structure than the one anterior.

The nucleus pulposus may be considered subject to the laws of fluids, that is, it is incompressible and confined to its normal shape and position by the strong bands of the annulus fibrosus. It has been compared to a system of hydrostatic ball bearings. Any compression of the disc must result, therefore, in changing the shape of the annulus fibrosus. The amount of compression which it will stand depends upon the elasticity and strength of this structure.

As regards the stability of this semi-fluid supporting structure, it is important to note that there is a strategic point of weakness posteriorly as compared with the anterior edge of the disc. Not only is there a lack of restraint from the bony rim ledge posteriorly but the concentric folds of fibrous tissue are fewer and thinner here. Also, the posterior longitudinal ligament is weaker than its anterior counterpart.

Fig. 10.

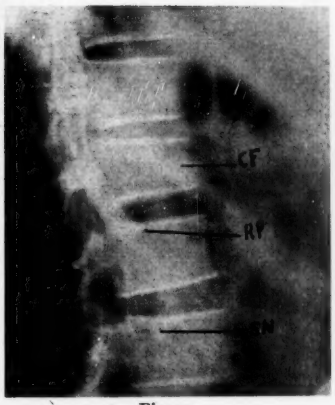


Fig. 11.

Fig. 12.

Fig. 10. Photograph of a sagittally cut section of the spinal column from the same patient as shown in Figure 9. In the lumbar region the discs, *D*, are seen almost to touch.

Fig. 11. A clinical roentgenogram showing a lateral view of the lower thoracic and upper lumbar regions of a patient who fell approximately 20 feet from a telegraph pole. Roentgenogram taken immediately after the accident was negative except for a compression fracture, *CF*, of the twelfth thoracic vertebral body, but this repeated view 3 months later revealed a rupture of the cartilaginous plate, *RP*, of the first lumbar body and a definite Schmorl's nodule, *SN*, in the second.

Fig. 12. Photograph of three macerated vertebræ showing typical depressions, *RP*, produced by prolapse of nuclear tissue into the spongiosa.

PATHOLOGY

1. Thick discs. At birth, the discs are relatively thick as compared with the height of the vertebral bodies. However, as the spinal column elongates with the advance in age, the discs gradually become relatively thinner (Fig. 8).

Also, in diseases which decrease the strength of the spongy bone, the pressure of the gelatinous nucleus in the intervertebral disc causes a bulging out into the adjoining vertebral bodies as is seen in such conditions as osteoporosis (Fig. 9), osteomalacia, cancer metastasis, and myeloma. In such cases the spongiosa may be so soft that the intervertebral discs almost touch (Fig. 10).

2. Thin discs. Much more frequently than thick discs, one sees thin discs in roentgenograms of abnormal spinal columns. Sometimes, the vertebræ appear almost to touch. It must be remembered that normally the intervertebral discs in the sacrum decrease during life until there is a complete disappearance except for the first sacral disc and sometimes the second, which may persist to old age. Occasionally a remnant of what might be considered a primitive disc separating the base from the body of the epistropheus remains until advanced age. With these exceptions, in any other part of the vertebral column, however, a change in height of the intervertebral space indicates a pathological change in the disc.

The decrease in water content of the disc which begins in the third and fourth decade, and all conditions which are collectively called degeneration, diminish the elasticity and make the disc thinner. Such transformations are usually accompanied by a color change in the disc substance, by cleft formation, and by fibrous tissue infiltration.

3. Displacement of the intervertebral disc tissue. The prolapse into the bony portion of a vertebral body (Figs. 11 and 12) which can be shown by roentgenogram, is now commonly referred to as a "Schmorl's nodule." This condition was first described by Luschka.

Schmorl believes that the importance of these nodules has been overemphasized in

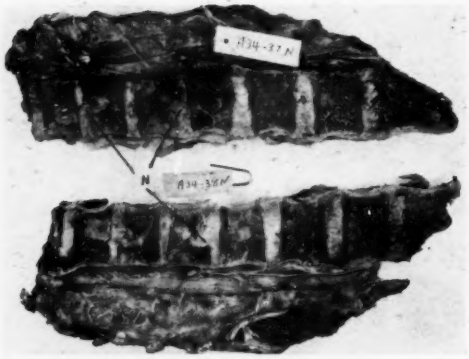


Fig. 13. Photograph of a portion of two spinal columns placed side by side for comparison. The one below shows carcinoma metastases, the one above multiple myeloma. A disc in the one below has been sufficiently weakened to permit rupture of the nucleus pulposus, *N*, into the spongiosa of an adjoining vertebral body. In the column above, 2 discs show slight narrowing with extrusion of some of their nuclear contents, *N*, into adjoining vertebral bodies.

Fig. 14. A posterior view of a section of the thoracic spine with the spinous processes removed showing a small rupture of the nucleus pulposus, *SN*, posteriorly into the vertebral canal. (No symptoms from pressure on the spinal cord were experienced by this patient.)

medicolegal cases. Furthermore, in this regard, it is well to remember that it requires several months before a diagnosis of a ruptured nucleus pulposus can be ruled out; this is because a prolapse of disc tissue into the spongiosa is not demonstrable immediately afterward. In fact, the first change after such an injury is a fibrous tissue reaction; this is replaced after about a month by a rim of cartilage which later shows a deposit of calcium sufficient in amount to be seen in a roentgenogram only after 3 to 4 months following the original injury.

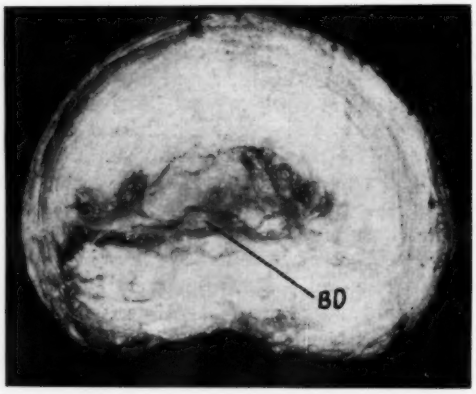


Fig. 15. Photograph of a horizontally cut intervertebral disc, showing brown degeneration, *BD*, from a woman 72 years old.

Therefore, final judgment regarding injury to a spine should not be rendered by a single X-ray examination when a displacement of disc tissue is a possibility.

The normal disc surfaces are thin where the nucleus pulposus bulges against them; it is here that less resistance permits rupture of disc substance into the spongiosa of the bodies. The causes of prolapse may be listed as follows: (1) The nucleus pulposus may follow old vessel channels which lead into the disc (Bohmig). (2) Degeneration may cause tears in the cartilaginous plates of old people. (3) Certain pathological processes may exist in the vertebral bodies in such conditions as tuberculosis, abscess formation, cancer metastasis (Fig. 13), Paget's disease, osteoporosis, myeloma, persisting notochord canal, or compression fracture which, in young people, may produce an irregular, jagged tear in the cartilage plate.

These displacements of disc tissue not only decrease the height of the disc but lessen its elasticity, lower its efficiency, and produce abnormal motion through release of pressure within the annulus—this may be compared to a partially deflated automobile tire. This may result in the grinding up of the remaining disc substance.

Posterior displacement of the nucleus pulposus may produce pressure on the spinal cord and lead to serious neurological disturb-

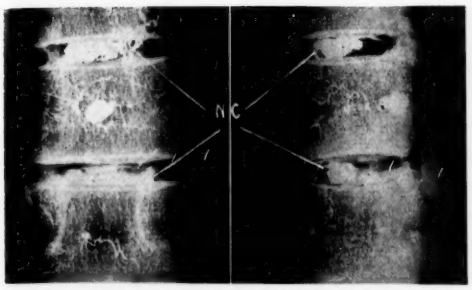


Fig. 16. Anteroposterior and lateral roentgenograms of the eighth and ninth thoracic intervertebral discs from a woman of 52 years showing the nuclear clefts, *NC*, of the upper disc injected with mercury and the middle one with lipiodol, demonstrating marked dilatation of the disc spaces. The blood vessels are injected with mercury.

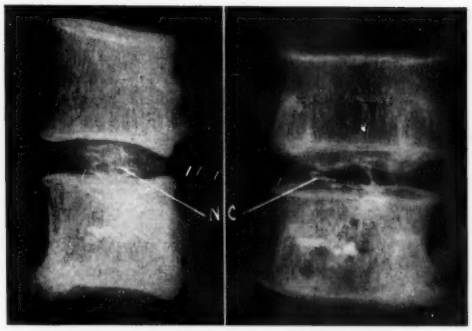


Fig. 17. Lateral and anteroposterior roentgenograms of an injected intervertebral disc from a woman 89 years of age showing the laminated appearance of the nuclear clefts, *NC*.

ances resembling a cord tumor, as reported by Dandy, and Barr and Mixter, or may produce no clinical symptoms whatever (Fig. 14) depending, of course, upon the size and location of the protruding mass of disc tissue.

4. Degeneration (drying out, grinding up, and deposition of pigment). Although the anatomical changes in the disc during degeneration vary greatly, they cannot be detected clinically except when they are accompanied by a decrease in height or by a deposit of calcium, which conditions may be shown by roentgenograms. In a young person, when the intervertebral disc is cut open, the gelatinous nucleus bulges out and appears moist; in an older person, it appears dry and yellowish or dark brown in color (Fig. 15). The composition of this pigment is not known; it does not give any reaction to the test for iron; for this reason it is believed to have no connection with blood. When the nucleus of an adult disc is injected with a substance opaque to roentgen rays, the resultant picture reveals a system of nuclear clefts, compared by one writer to the spaces between the lamellated layers of an onion; these are always much dilated in old people (Figs. 16 and 17).

The grinding up of the intervertebral disc tissue produces large cavities in the interior (Fig. 18), while the outermost periphery of the fibrous ring remains intact. Such resultant cavities are lined with a gray, dry, crumpled tissue which is the former disc substance dried up and ground up. Occasionally concentric tears are found in the fibrous layers near the edge parallel to the rim ledge.

It is interesting in this regard to note that in hard working people, Schmorl reported well preserved discs even in the aged, whereas, in people who had sedentary occupations, strangely enough, more often degenerative changes were found. He believed that ordinary trauma in daily work plus the individual constitutional factors, which vary greatly in different individuals despite occupation or walk of life, play a more effective rôle than disease processes in producing these degenerative changes. At least this was the conclusion he was forced to take in trying to interpret his own statistical records.

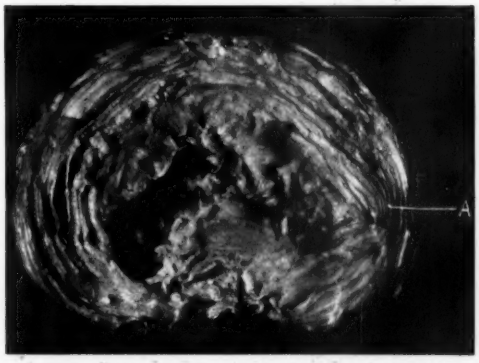


Fig. 18. Photograph of a horizontally cut disc from a woman 85 years old. Only the outer layers of the fibrous ring, *A*, remain. The gelatinous nucleus and inner parts of the fibrous ring are ground up and destroyed.

Fig. 19. A clinical roentgenogram of the thoracic vertebral region in a patient who shows calcification, *K*, in one intervertebral disc; it should be noted here that practically every cartilaginous plate has been ruptured.

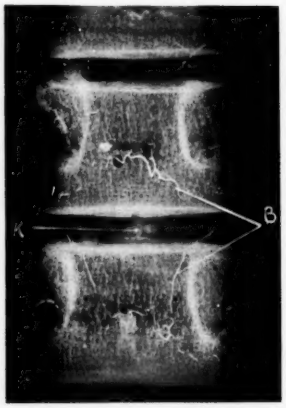


Fig. 21. An anteroposterior roentgenogram of the same section of spine as in Fig. 20, showing bony spicules, *K*, in the annulus fibrosus. (The vessels, *B*, are shown injected with mercury.)

5. Calcifications. Calcifications may appear in the cleft regions of the gelatinous nucleus as cloudy, spotty, branched shadows usually in the central portion of the disc with several processes projecting outward, but they appear more frequently in the periphery of the fibrous ring. They can be demonstrated easily by roentgenogram (Fig. 19). From 200 carefully studied vertebral columns of all ages, Ratheke calculated that 71 per cent of these showing lime deposits were in the annulus and 6.5 per cent in the nucleus. The incidence of these deposits increases with age. The etiology is generally regarded as a degeneration phenomenon, except in the so-called "secondary calcifications" following healing inflammatory reactions (tuberculosis); but further research is necessary to show whether they are merely calcified hematomas.

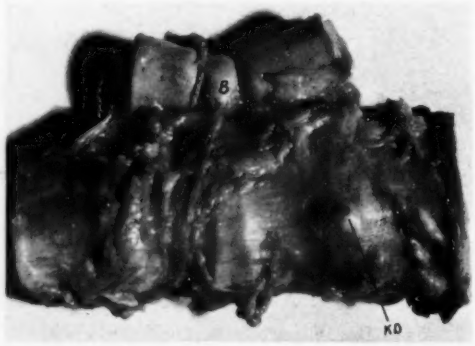


Fig. 20. Photograph of the anterior aspect of a spine just as it appeared when removed at autopsy from a woman 52 years of age. A calcium deposit, *KD*, may be seen projecting between the tenth and eleventh thoracic vertebræ. (A tied off portion of the aorta, *B*, above was retained here for the purpose of injecting the arteries with mercury.)

6. Deposits in the intervertebral discs of other kinds of tissues. Fibrous tissue has been reported found in the gelatinous nucleus pulposus at necropsy. Such deposits destroy the normal stratification of the nucleus and possess very little elasticity. Clinically, one finds a decrease in the height of the disc.

Blood vessels occasionally occupy a considerable part of the gelatinous nucleus and fibrous ring. Connective tissue generally accompanies these vessels which arise usually from the surfaces of the vertebral bodies. The borderline between the disc and the ingrowing blood vessels is quite distinct. This invading tissue may not always be in the gelatinous nucleus but may be in the annulus. Here it represents a process of healing concentric tears in the outer portions of the fibrous ring.

The ingrowth of blood vessels and fibrous tissue is often accompanied by bone formation. The intervertebral disc may be completely replaced by spongy bone as in the congenital "block vertebra." Sometimes a little remnant of the disc tissue may be present.

Occasionally the region of the annulus may be filled with spongiosa while the mid-portion of the disc still contains the gelatinous nucleus. Because they are sometimes confused with fractures of the rim ledge, it is important from the standpoint of differential diagnosis to distinguish between these deposits of calcium in the annulus following little tears in the fibrous ring. Such deposits occur most frequently on the anterior border, parallel to the stratification of the fibrous ring, and may be quite large (Figs. 20 and 21).

The author is indebted to Dr. Frank R. Ober for his helpful suggestions in directing this work, to Dr. Sidney Farber for the use of his laboratory, and to Dr. G. Kenneth Coonse for permission to use two of his clinical X-ray pictures.

BIBLIOGRAPHY

1. Barr, J. S., and Mixter, W. J. Rupture of the intervertebral disc with involvement of the spinal canal. New England J. Med., 1934, 211: 210.
2. Beadle, O. A. The Intervertebral Discs. Observations on their Normal and Morbid Anatomy in Relation to Certain Spinal Deformities. Medical Research Council, Special Report Series, No. 161, London, 1931.
3. Dandy, W. E. Loose cartilage from intervertebral disc simulating spinal cord tumor. Arch. Surg., 1929, 19: 660.
4. Keyes, D. C., and Compere, E. L. Normal and pathological physiology of nucleus pulposus of intervertebral disc. J. Bone & Joint Surg., 1932, 14: No. 4.
5. Ratheke, L., Ueber Kalkablagerungen in den Zwischenwirbelscheiben. Fortschr. d. Roentgenstr., 1932, vol. 45.
6. Schmorl, G., and Junghanns, H. Die Gesunde und Kranke Wirbelsaenle in Roentgenbild. Leipzig: Georg Thieme, 1932.

GASTROJEJUNAL ULCER AND GASTROJEJUNOCOLIC FISTULA

FRANK H. LAHEY, M.D., F.A.C.S., and NEIL W. SWINTON, M.D., Boston, Massachusetts

In 1928 one of us (FHL) and Dr. Sara M. Jordan, published a survey of the literature on gastrojejunal ulcer and reported cases from this clinic.[1] About one thousand cases had then been reported but gastrojejunal ulcer was not accepted at that time by many surgeons as a common complication of anastomosis of the jejunum to the stomach. In the years 1928 to July, 1934, there have been 1,089 cases of gastrojejunal ulcer reported in the literature.

It is interesting to note that gastrojejunal ulcer is now considered a serious and not unlikely complication of any operative procedure for ulcer in which the stomach is anastomosed to the intestine, and not a sequela peculiar only to gastro-enterostomy.

INCIDENCE

As can be seen in Table II the reported incidence of gastrojejunal ulcer varies greatly. The range for gastrojejunal ulcer following gastro-enterostomy is from 1.7 per cent (Walton) to 24 per cent (Strauss, Block, Friedman). With resections there is also a wide disparity in its incidence from 0.4 per cent (Schwarz) to 10 per cent (Gatewood.) It is noteworthy that the German investigators report a very low incidence of marginal ulcer following resection. Fohl ascribes these variations in incidence to incomplete follow-up studies and possibly to the number of ill-advised operations rather than to constitutional characteristics or operative technique.

Hurst and Stewart believe that the incidence of gastrojejunal ulcer is greater than is reported, and base their opinion on results of a statistical study of postmortem examinations at the New Lodge Clinic. In a series of 10,300 autopsies, there were 131 on patients who had had operations for ulcer. Of these, 46 patients died within 10 days of the operation for ulcer and in these patients there were no gastrojejunal ulcers. In 41 cases death occurred from 10 days to 2 months after operation. In this group there were 3 gastrojejunal ulcers. In 43 cases in which death occurred 9 months after operation, there were 22 cases of ulcer. All of these gastrojejunal

[1] Lahey, Frank H., and Jordan, Sara M. Gastrojejunal ulcers and gastrojejunocolic fistulæ. Ann. Surg., 1928, Feb.

TABLE I

Name	Cases	Total
1928		
Allen	11	
Balfour	6	
Broster	6	
Budde	1	
Deaver	1	
Ehrlich	1	
Grassmuch	1	
Hurst, Stewart	44	
Jones	36	
Leplat	1	
Lauria	2	
Nixon, Lowry	1	
Porzelt	1	
Eusterman	1	
Robinson	1	
Schwarz	1	
Strauss, Block, Friedman	5	
Strelinger	10	
Thompson, Stewart	1	131
1929		
Bager	31	
Balfour	31	
Cabot Case	1	
Fremont-Smith	14	
Fromme	2	
Gottstein	1	
Hayon	12	
Hinterstoisser	1	
Judin	1	
Just	1	
Leriche	1	
Luff	28	
Simon	1	
Sole	3	
Urrutia	229	
Weir	33	390
1930		
Balfour	16	
Bromley	1	
Douglas	12	
Elansky	13	
Finney, Hanrahan	20	
Gatewood	9	
Haberer	121	
Hartwell, Felter	2	
Horsley	3	
Judine	14	
Lewisohn	5	
Neller	3	
Oberniedermayr	4	
Starlinger	17	
St. John	10	
Walton	44	294
1931		
Allen	21	
Charrier	2	
Davenport	1	
Down	3	
Finsterer	7	
Hinton	7	
Judin	2	
Lewisohn	1	
Lublin	10	
Russell	1	
Smyth	1	
Steden	4	
Viviana	5	
Walzel	1	
Woodside	1	
Zukschwerdt, Eck	11	78
1932		
Bertrand, Martin	1	
Braine	2	
Brandtner, Tonnis	2	
Buckstein	3	
Caucci	1	
Connell	1	
Estes	2	
Macguire	1	
Prickman	1	
Valdoni	52	66
1933		
Andrews	1	
Balfour	1	
Benedict	36	
Hinton	3	
Lamson	1	
Mallet, Guy	1	
Meyer, Rosi	1	
Miller, Holmes	2	
Strode	1	
Willis	1	48
1934		
Steinberg	1	
Wilkie	2	
Walton	79	82
Total number of Cases		1,089

SUMMARY

1928	131	1932	66
1929	390	1933	48
1930	294	1934	82
1931	78		
		Total	1089

ulcers (25) were in 30 cases of duodenal ulcer, an incidence of 73 per cent. From these figures the total incidence of gastrojejunal ulcer in 131 ulcer operations is 19 per cent.

Because of the high incidence of gastrojejunal ulcer after operations in which the pylorus is separated and occluded (20 per cent Makkas, Leriche, v. Haberer), operations of that type (such as von Eiselsberg's exclusion) have largely been abandoned. It is difficult to compare the incidence of recurrence of ulcer after anterior and posterior gastro-enterostomy, although most authors state that recurrence is more frequent after anterior anastomoses. However, Walton in 1,313 posterior anastomoses found 29 gastrojejunal ulcers while in following 33 patients with anterior gastro-enterostomies there were no marginal ulcers. Fischer believes that postoperative ulcer does not occur more often following anterior gastro-enterostomy and urges its use to avoid the complication of fistula into the colon. (Gastric jejunocolic fistula) Allen believes that marginal ulcer occurs as frequently after resection as after gastro-enterostomy and in addition a secondary operation is more difficult after a resection.

In a paper by Dr. Roscoe R. Graham, of Toronto, Canada, read at the last meeting of the American Medical Association and kindly made available for us by Dr. Graham before its publication, the results of a series of gastric operations as relates to gastrojejunal and jejunal ulcer are presented. These results are based upon 43 cases of which 33 were personally operated on by Dr. Graham. This included 4 cases of gastrojejunocolic fistulas. Of the 43 cases, 4 cases, they state, had been studied and confirmed by X-ray examinations but not yet operated upon. Six were cases of associates. Five of these 6 cases were proved by operation and one confirmed by X-ray.

In a series of 5 cases in which the stomach was cut across at its middle, the distal end turned in, and the jejunum anastomosed to the proximal end, the so called Devine procedure, he surprisingly reports the development of 5 jejunal ulcers in a relatively short time.

Three cases are reported in which the gastroenterostomy was taken down with excision of the ulcer, repairing the defect in the duodenum.

thus restoring the alimentary canal to its original state. All 3 cases, he states, are now suffering severely from duodenal ulcer symptoms.

Of 28 cases with primary pyloroplasty for duodenal ulcer, the author states that in subsequent X-ray studies in none did they find normal gastric motility. They report constant hyperperistalsis and state that the patients have not had brilliant clinical cures.

In 9 cases in which the stomach was anastomosed to the duodenum (gastro-duodenostomy), there was one fatality and 4 instances of marginal ulceration at the stoma.

In 4 cases in which the gastro-enterostomy was taken down, the jejunum restored, a partial gastrectomy done, and the end of the stomach anastomosed to the second part of the duodenum, there were 3 instances of ulceration at the new stoma.

In 1 case a partial gastrectomy was done with restoration of the jejunum, an anterior Pólya anastomosis and an entero-enterostomy with the development of an ulcer in the efferent loop of the Pólya gastrojejunostomy.

They report no recurrences after gastric resection, restoration of the jejunum, and end-to-end anastomosis of the cut end of the stomach to the duodenum and no recurrences following resection and posterior Pólya anastomoses.

The figures of Hinton and Church published 1 month ago are of great interest because of the fact that all of the cases have been so well worked up and so carefully followed. The report is from the Fourth Medical and Surgical Division of Bellevue Hospital. Ninety patients of all the admissions for ulcer from January 1, 1928, to January 1, 1933 had been operated upon. Of these 79 had had gastro-enterostomy. Of these 79 patients having had gastro-enterostomy, 13, or 16.4 per cent, had gastrojejunal ulcer. Of these patients considered to have gastrojejunal ulcer, 6 were proved by operation to have it and 7 by X-ray evidence to have it, and it must be admitted from the convincing X-ray evidence which is recorded in each case that it seems likely that the diagnosis was correct also in these cases.

Walton states: "There seems no doubt that a partial gastrectomy does not give a complete immunity to the onset of the gastrojejunal ulcer; but it is less frequent after this operation (about 0.5 per cent) than after gastro-enterostomy." He states: "My own belief is that, provided sufficient of the stomach is removed to produce achlorhydria, the complication is almost unknown, although the risk of subsequent anemia may be increased thereby."

Our own experience with gastrojejunal ulcer and gastrojejunal colic fistula deals with 30 gastrojejunal ulcers and gastrojejunocolic fistulas of which 13 were uncomplicated gastrojejunal ulcers and were operated upon. The immediate mortality in this group was 2 cases, 15 per cent. Of the 13 patients operated upon, 10 had excision of the gastro-enteros-

TABLE II.—INCIDENCE OF GASTRO-JEJUNAL ULCER

Year	Name	Gastro-enterostomy			Resection		
		No. of gastro-enterostomies	No. of anastomatic ulcers	Per cent	No. of operations	No. of anastomatic ulcers	Per cent
1928	Rowlands			2			
	Schwarz			3–5	210 (Reichel)	1	0.4
	Strauss						
	Block			24	Pólya		1
	Friedman						
1929	Balfour	491		3.26			
	Luff	744	21	2.8			
	Weir				418	33	7.8
1930	Berg						1.1
	v. Haberer				2,310	15	0.6
	St. John	119		6.9	76		3.6
	Walton	981	44	1.7			
	Neller				43	3	7
	Starlinger				25,647*	173	0.7
	Gatewood	146	9	6	30	3	10
1931	Charrier	60	2	3.3			
	Pauchet			5			
1932	Fischer						1.5–‡ 5.6
1933	Benedict	732		2.9			
1934	Wilkie			3.5			
	Walton	1,576	30	1.69	326	2	.61
	Hinton	79	13	16.4			

*From 85 institutions.
‡From literature.

tomy, resection of the jejunum, anastomosis of the jejunum, and restoration of the alimentary stream to its normal state. Of the 10 patients having this operation, 40 per cent or 4 have had recurrent duodenal ulcers. Of these 4, 1 died later of an acute perforation, 1 had severe symptoms of duodenal ulcer 11 years afterward, but had not been able to follow a careful regimen, 1 was well for 4 years and then had a serious hemorrhage, and on 1 a radical subtotal gastrectomy was done (FHL) 2 years after the conservative operation.

Of this group there are 9 patients with gastrojejunocolic fistula, 1 of whom refuses operation and 8 have been operated upon. The immediate mortality was 63 per cent, the cause of death being in 1 case, peritonitis; in 2 pneumonia; 1 was a cardiac failure, and 1 was due to obstruction and pneumonia. Of the living cases of gastrojejunocolic fistulas, 1 patient is perfectly well 5 years after operation but on a strict diet, 1 is well at the end of 2 years, 1 died of obstruction 4 months after leaving the hospital, and the 1 who refused operation has been followed 8 months, and is having one to two stools a day and is in excellent health.

There are 8 cases proved by X-ray diagnoses and histories of gastrojejunal ulcer in which operation was not done, of these 3 are well 6, 8, 12 months, respectively, after first being seen and placed on treatment. One has now gone 4 years but has severe ulcer symptoms which can in a considerable measure be controlled by treatment, 1 has been under observation but 6 months and is unable to work, 1 died from an acute perforation 2 years after being on treatment, 2 are well but have had serious hemorrhages 1 at 2 years and 1 at 4 years after the onset of symptoms. It must be admitted, I think, that there are some patients with gastrojejunal ulcer and also a few with gastrojejunocolic fistulas who can be carried along satisfactorily under medical measures.

AGE

The age incidence depends upon the age at which the primary operation was done, but in a large majority of the cases listed the patients are in the age period from 30 to 45 years. The youngest in this survey was in a boy of 10 years, reported by Strode. From three-fourths to four-fifths of all cases reported are in men. (Hayon). In our series there were 90 per cent males and 10 per cent females.

PATHOLOGY

The postoperative (gastrojejunal) ulcer occurs for the most part at one of two sites—either at the stoma itself or in the efferent loop of the jejunum in the neighborhood of the anastomosis, often opposite the new opening. They are all in the jejunum either marginal to the new opening or at a little distance from it. Gastrojejunal (marginal) ulcer is found in 75 per cent of the cases, and jejunal in 25 per cent (Urrutia, Starlinger).

They are similar pathologically to primary peptic ulcers, in that they are sharply demarcated and are very vascular. Ulcers of small size show a very intensive proliferative reaction about them which results in a definite tendency to penetration into neighboring organs. The earlier authors reported the incidence of perforation in gastrojejunal ulcers as 20 to 25 per cent. However, Gottstein, Just, Gosset, Bertrand, Martin all believe that it is comparatively rare. Starlinger reported the number of collected cases of free perforation as 150. On the basis of 2,500 cases of gastrojejunal ulcer reported after gastro-enterostomy and 300 after resection, he estimated the percentage of perforations as 5.6 per cent after gastro-enterostomy and 3.3 per cent after resection. The percentage of perforation in our series was 9 per cent.

Makkas (1934) collected 170 cases of free perforation from the literature. He believes that perforation occurs less frequently in gastrojejunal than in primary peptic ulcer, probably because the severity of the symptoms leads patients with gastrojejunal ulcer to seek help from surgical treatment earlier than do those with duodenal and gastric ulcer. This complication occurs most often in jejunal ulcers (Bager, Makkas). Gastrojejunal ulcers show a considerable tendency to hemorrhage, in our series 13 per cent.

ETIOLOGY

Numerous theories have been proposed to explain the occurrence of gastrojejunal ulcer.

Among these are ulcer diathesis, hyperacidity, infections, poor surgical technique and the lack of medical care.

One of the most fundamental of these theories is that of ulcer diathesis, a constitutional tendency on the part of an individual to develop ulcer. This tendency is particularly evident in this group of patients with gastrojejunal ulcers in many of whom a series of operations had been done for recurrent ulcer. A brief history of one of our own cases illustrates this point:

Mr. R. A. A gastro-enterostomy was done on this patient by one of us (FHL) for duodenal ulcer in 1917 with the development of a gastrojejunal ulcer which was operated on by FHL in January, 1928. The ulcer, gastro-enterostomy opening, and a section of the jejunum were removed, and the alimentary canal restored to the original course with the immediate development of an active duodenal ulcer with bleeding that required further operative procedure. In May, 1929 the stomach was cut across at its center, a large section of stomach removed, the jejunum anastomosed end-to-side to the proximal cut end of the stomach and the distal cut end turned in (Devine operation). No attempt was made to remove the ulcer because of the immense amount of induration about it. Following this operation, there have still been ulcer symptoms associated with gastric hemorrhages. This patient seen 2 days ago, 5 years after operation, has gained 18 pounds in weight but requires strict adherence to a limited diet to remain free from ulcer symptoms.

High family incidence is another indication of this tendency. Allen reported a family in which the father and 5 sons all had an ulcer history, with numerous operations. Hurst and Stewart found that in 6 of 43 cases there were 2 or more near relatives who had gastrojejunal ulcer. Jones also found a striking family incidence of ulcer in a group of cases of gastrojejunal ulcer.

A significant contribution to the possible etiology of gastrojejunal ulcer has been the explanation according to the biochemical theory of the nature and location of ulcer lesions.

Buencher has pointed out that areas in the stomach which secrete acid gastric juices are somewhat resistant to ulcer formation, while areas of gastric activity protected only by the mildly alkaline mucous production are highly susceptible to ulcer formation.

After operative procedures such as gastro-enterostomy where the jejunum is brought into contact with an area of gastric activity near the pyloric end of the stomach, a severe jejunitis occurs according to Konjetzny and Puhl. This is shown by increased connective tissue in the submucosa, definite dilatation of vessels, and the infiltration of surrounding tissues with inflammatory cells.

However, Walters believes that the type of ulcer seen in Germany is different from that commonly seen in this country, being characterized by multiplicity of ulcers and extensive erosions. These changes, regarded as characteristic by German authors, he has found in very few patients in this country. He raises the question as to whether the small percentage of recurrences after gastro-enterostomy reported by some authors in this country may not be in cases in which such a gastritis has occurred.

At von Bergmann's clinic changes in the mucous membrane of the jejunum have been noted in all cases of gastrojejunal ulcer.

One might suppose that some light on the causation of postoperative ulcer might arise from a study of primary jejunal ulcer but such is not the case. While this lesion is unusual, Ebeling in 1933 reported 47 cases collected from the literature. This condition occurred in the 40 to 60 year group, with a preponderance of 3 to 1 in males. The history was of dyspepsia, often simulating a duodenal or gastric ulcer history. The ulcers were located in the upper or middle jejunum and were similar pathologically to gastric or duodenal ulcer. Any specific cause was eliminated in the cases reported as far as possible. That an excess of acid secretion may be a factor is suggested by the case of Holzweissig mentioned by Morrin, in which 8 ulcers occurred in the jejunum in the presence of a complete obstruction by a stone at the ampulla of Vater.

HYPERACIDITY

Unquestionably, hyperacidity plays a prominent rôle in the etiology of gastrojejunal ulcer. There are numerous clinical and experimental observations which indicate the importance of this factor.

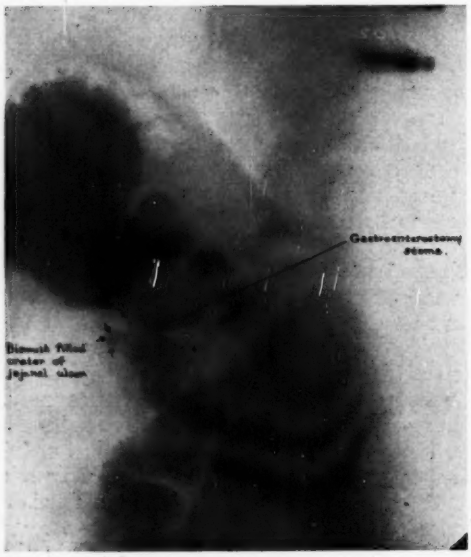


Fig. 1. The X-ray print which was reversed in printing demonstrates very clearly the bismuth filled crater of a post gastroenterostomy jejunal ulcer. The ulcer may be seen as a diverticulum-like projection from the jejunum just beyond the point where the jejunum has been anastomosed to the stomach bearing out the statement in the text that these ulcers are all jejunal, 75 per cent being marginal to the gastro-enterostomy and 25 per cent in the jejunum at varying distances from the stoma.

1. Gastrojejunal ulcer occurs but rarely in women. Lerman, Pierce, and Brogan after histamine and alcohol tests found that in a normal group, males show a higher acidity range than females.

2. Gastrojejunal and postoperative jejunal ulcer almost never occurs after gastro-enterostomy for carcinoma, a condition in which anacidity is usually present.

3. The primary ulcer in a large proportion of cases is duodenal. In our series the primary ulcer was duodenal in 90 per cent of the cases and gastric in 10 per cent. Hurst and Stewart found that 61 per cent of duodenal ulcers were accompanied by hyperacidity while only 29 per cent of gastric ulcer showed increased acidity.

4. Gosset found that 80 per cent of his cases of gastrojejunal ulcers had hyperchlorhydria. Jones found that 74 per cent were above the normal level. In our series 95 per cent of our cases had a hyperchlorhydria. In those patients in our series with a gastrojejunocolic fistula but 50 per cent had a hyperchlorhydria.

5. Rivers and Wilbur reported 7 cases in which gastro-ileostomy had been done by mistake before the patients came into their hands. In 2 of these, ulceration was present in the ileum. Their conclusion was that peptic lesions may arise in any situation in which gastric juices are allowed to come into contact with intestinal mucosa.

6. Indirect evidence is afforded by a case reported by Morton and Graham. A patient had been operated upon for cholelithiasis. After operation she had a large hemorrhage and died. At postmortem examination a large duodenal ulcer was found and two stones blocking the bile duct and the pancreatic duct so that no alkaline digestive juices were reaching the pylorus.

7. Owings and Smith repeated the experiments of Mann and Williamson and reported that 10 of the 26 dogs developed ulcers of the jejunum when the jejunum was deprived of the alkaline digestive juices. Their work indicated that bile was the most important element in the neutralization of acid chyme.

8. That the influence of acid secretions is not the sole factor is suggested by the case which Eusterman reported in which gastrojejunal ulcer developed in the presence of persistent achlorhydria.

INFECTION

The influence of foci of infection on the causation of ulcer is generally accepted if not proved.

Hurst feels that infection is the most important exciting cause of gastrojejunal ulcer. The focus may be in the teeth, pharynx, sinuses, appendix, or gall bladder, or in a gastric or duodenal ulcer which has not healed. In his series of 36 cases, he found only 2 with normal teeth.

Wilkie believes that ulcer can be considered one of many septic foci and no treatment is of lasting benefit until these foci are removed. He stresses particularly dental infection.

Saunders reports the recovery of a streptococcus from 16 cases of resected gastroduo-

denal and gastrojejunal ulcers, which was identical and specific by differential cultural and agglutination tests. The growth of the organism was inhibited by bile.

POOR SURGICAL TECHNIQUE

The most frequently mentioned possible causative factors in surgical technique in the production of postoperative gastrojejunal ulcer are the use of non-absorbable sutures, the use of clamps, and the improper placement of the anastomosis.

Scott, by clinical and experimental records, showed that sutures did not influence the occurrence of ulcer. In our earlier paper on this subject (Lahey and Jordan), it was likewise our conclusion that suture material played no part in the production of ulcer. The frequency of postoperative ulcer has increased in recent years despite the general abandonment of non-absorbable sutures. Several cases are reported in which strands of suture were found hanging from the anastomosed mucosa in the complete absence of any ulcer. Any ulceration at the stoma will of necessity erode down to the suture line and if it is of linen or silk this will be visible in the ulcer base.

Andrews does not believe that sutures have any influence. Walton states that the use of catgut may reduce the incidence, but it will not abolish it.

Willis states that "from later observations it is likely that silk or linen suture is simply a bystander and not the cause of the lesion."

Tight clamps are seldom used in operations on the stomach at the present time, so that their influence on the formation of ulcers is probably negligible.

In regard to operative trauma, Balfour is convinced that some recurrences are due to the devitalization of the suture line. This, however, does not explain the occurrence of gastrojejunal ulcer 10 to 15 years after the gastro-enterostomy.

The position of the anastomosis high on the gastric wall theoretically leads to stagnation of the stomach contents and poor emptying. Hartwell and Felter do not think the location of the gastro-enterostomy opening has either an important clinical or mechanical influence

Fig. 2. The X-ray print needs very little explanation. This is a bismuth enema in a patient with a large gastrojejunocolic fistula in which all of the structures can be readily recognized. Note the size of the fistula into the colon. Note the large amount of bismuth in the stomach and its fluid level. From this amount of bismuth it must be concluded that the caliber of the fistula must be considerable.

as they found patients in their follow up study by X-ray examination who had high openings but no complaints and satisfactory emptying time. Benedict reported a case in which recurrence of ulcer followed 18 years of freedom from symptoms in which the stoma was located high on the gastric wall. We have had a patient in whom gastrojejunal ulcer occurred 17 years after a gastro-enterostomy.

These opinions together with some of our experiences and excerpts from a further review of the literature (1928–1934) are recorded in order that readers may have some idea of the conflicting opinions and variety of theories available in connection with this subject.

SYMPTOMS

The time of onset of symptoms of gastrojejunal ulcers varies from a few weeks to many years, up to 21 years (Lublin). In 50 cases

taken at random, 50 per cent of the recurrences, (gastrojejunal) occurred within 2 years following operation.

In general it may be said that the longer period patients who have had anastomoses of the jejunum to the stomach go without recurrence of ulcer symptoms, the less likelihood is there of the occurrence of gastrojejunal or jejunal ulcer. One must assume, in spite of this, however, that in any patient who has had the jejunum anastomosed to the stomach, the development of a gastrojejunal ulcer is always possible regardless of the time factor.

There are certain features of the symptomatology of gastrojejunal ulcer which are characteristic of this condition. In patients who have developed postoperative gastrojejunal ulcer, there is usually a period after the performance of the gastro-enterostomy in which the patient is entirely relieved of the ulcer symptoms for which the operation was done, with a later return of ulcer symptoms not infrequently of greater intensity than the original symptoms for which the operation was done. The ulcer pain is less satisfactorily relieved by food and alkalines than was the pain associated with the original ulcer. The pain is less consistently related to meals than was the original ulcer pain. The distress associated with the occurrence of gastrojejunal ulcer is less tractable to all methods of treatment than was the distress associated with the original ulcer.

Hemorrhage and melena are, we believe, somewhat more frequently associated with marginal ulcer than with the duodenal and gastric ulcer.

The point of abdominal tenderness in duodenal ulcer (and duodenal ulcers make up the great majority of ulcers, 10 duodenal to 1 gastric ulcer in our experience) is usually in the right upper quadrant while in gastrojejunal ulcer the point of abdominal tenderness tends to be lower down a little above and to the left of the umbilicus. This is the point on the abdominal wall opposite which the anastomosis of the jejunum to the stomach commonly rests and with gastrojejunal ulcer it is usually tender over the stoma here.

Symptoms of ulcer perforation in any patient who has had a gastro-enterostomy performed particularly for duodenal ulcer should make one suspect the possible presence of a perforated gastrojejunal ulcer.

DIAGNOSIS

The recurrence of symptoms suggestive of ulcer after operative measures for ulcer, particularly duodenal ulcer, should always suggest the probability of gastrojejunal ulcer. The presence of tenderness over the stoma on fluoroscopic visualization of the stoma likewise suggests it. The presence of a fleck at the stoma after the ingestion of a small amount of barium suggests that this is due to a small amount of bismuth remaining adherent to the ulcer (Fig. 1). The presence of a gastrojejunocolic fistula demonstrable by X-ray definitely settles the diagnosis of gastrojejunal ulcer (Fig. 2).

The closure of the stoma likewise suggests the presence of a gastrojejunal ulcer, as does persistent deformity of the stomach, stoma or jejunum.

PROPHYLAXIS

There is probably no really effective prophylaxis against the possible occurrence of gastrojejunal ulceration following anastomosis of the jejunum to the stomach. Exclusive of the immediate technical steps of the operation of anastomosis of the jejunum to the stomach such as tight sutures, tight clamps, and nonabsorbable sutures all of which can as already stated probably be excluded, there are a number of things which at least are factors favorable to the postoperative occurrence of a gastrojejunal ulcer.

We have repeatedly stated that any patient who has an anastomosis of his jejunum to the stomach should be told of the danger of postoperative marginal ulcer. He should be told of the seriousness and intractableness of such a complication and the need for permanent modification of eating, drinking, smoking, and living habits after any gastric operation for peptic ulcer. There has very definitely been an improper tendency to let patients assume that one of the rewards of a successful operation for peptic ulcer is that they escape the necessity of the above mentioned irksome modification of life habits. Unless such a warning is given patients, should a recurrent

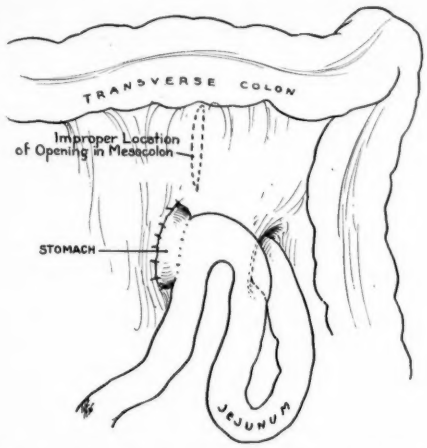


Fig. 3. This illustration shows diagrammatically the proper and improper location of the opening in the gastrocolic omentum for a gastro-enterostomy. One can appreciate when the opening is made as shown in dotted lines close to the transverse colon, that should a gastrojejunal ulcer occur, it almost must involve the transverse colon in the surrounding exudate and so penetrate frequently into the colon and produce a gastrojejunocolic fistula. This drawing illustrates a jejunal loop of sufficient length to permit easy resection an anastomosis should a jejunal ulcer occur as opposed to the no-loop type of jejunal anastomosis.

gastrojejunal ulcer occur, no surgeon's conscience can be entirely free from responsibility for this recurrence. While no statistical figures are available as to the incidence of gastrojejunal ulcer following gastro-enterostomy in patients with well controlled postoperative habits and diets as opposed to those with uncontrolled habits and diets, it is not unreasonable to assume as distinctly probable that the incidence of gastrojejunal ulcer will be less in those patients with gastro-enterostomies whose habits and diets are controlled than in those whose habits and diets are not controlled. This we have always maintained is perhaps a small but important factor in the postoperative incidence of gastrojejunal ulcer.

There are a few general surgical principles which probably influence the occurrence of gastrojejunal ulcer.

It is generally accepted that gastrojejunal ulcer is more apt to follow the employment of gastro-enterostomy in young individuals with high gastric acids and active ulcer symptoms

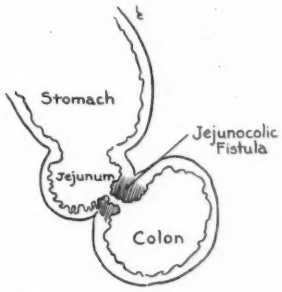


Fig. 4. This drawing indicates diagrammatically how the colon becomes adherent to the jejunum and the ulceration breaks into it.

than in older people without strikingly high acids.

It is generally felt (as stated from the literature in this and our original paper) that to make a gastro-enterostomy and then to obstruct the pylorus preventing thus the regurgitation of alkaline duodenal contents into the stomach increases definitely the risk of gastrojejunal ulcer.

It is believed and is probable that to do entero-enterostomy between the afferent and efferent loop of a jejunum anastomosed to the stomach, sidetracking as it does the passage of alkaline jejunal contents from going back into the stomach through the new opening, likewise predisposes to an increased danger of the formation of a gastrojejunal ulcer.

It has been quite definitely demonstrated by animal experiments that the lower the level in the jejunum at which that structure is anastomosed to the stomach, the easier it is to produce intestinal ulceration since adaptability to receive unneutralized acid gastric contents is less and less well developed the further away that level is from the duodenum. For this reason, while no convincing figures are available to prove it, it is believed that anterior gastro-enterostomy requiring as it does anastomosis of the jejunum at a much lower level in the jejunum than is necessary with posterior gastro-enterostomy is perhaps followed by a few more gastrojejunal ulcers than is posterior gastro-enterostomy. (Walton's figures of 33 cases with no gastrojejunal ulcers are suggestive but too small a series to be of great value.) On purely theoretical grounds

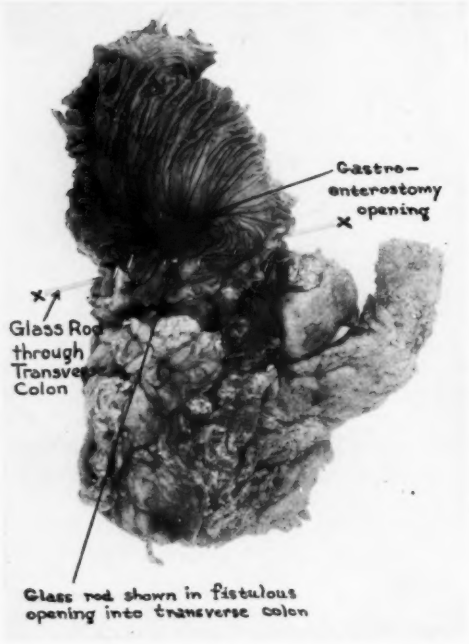


Fig. 5. This is the resected stomach of the patient whose X-ray film is shown in Figure 1. The stomach is shown with the gastro-enterostomy presenting. A glass rod has been passed through the attached transverse colon, $x-x$, and in the gastro-enterostomy stoma the rod may be seen at the point where the jejunal ulcer has eroded into the colon. Although the photograph does not demonstrate it well, one can from this picture of the block of tissue removed, stomach, colon and jejunum, get some idea of the amount of induration present.

if it could be proved that gastrojejunal ulcer was no more common following this operation than posterior gastro-enterostomy would be a safer operation than posterior gastro-enterostomy since, because of the position of the colon, gastrojejunocolic fistula with its high mortality is anatomically less apt to occur after anterior gastro-enterostomy than after posterior gastro-enterostomy and should gastrojejunal ulcer occur after anterior gastro-enterostomy, it would be infinitely easier and safer to manage surgically from a technical point of view than is gastrojejunal ulcer in posterior gastro-enterostomy. Should a gastrojejunal ulcer occur with an anterior gastro-enterostomy, it occurs on the anterior wall of the stomach where it is easily approached and in addition there is a long loop of jejunum available permitting the ready excision of the segment anastomosed to the stomach and with sufficient length of proximal jejunal stump so that end-to-end anastomosis can easily be done.

One of the greatest technical difficulties in dealing with gastrojejunal ulcer in posterior gastro-enterostomy, particularly if of the so-called no loop type, is that the induration about the ulcer involves the root of the jejunal mesentery at the level of the ligament of Treitz making separation of the jejunum and the handling of its mesentery with its blood supply difficult, and the other is that when the jejunum is separated from the stomach if complete resection of a segment of jejunum is necessary, such a small intraperitoneal proximal stump of jejunum sometimes remains that end-to-end anastomosis is often difficult and far from satisfactory.

It is definitely the opinion of one of us (FHL) that were he to select the type of gastrojejunal ulcer he preferred to deal with from his operative experiences with gastrojejunal ulcer, he would select a gastrojejunal ulcer in an anterior gastro-enterostomy and, if he had to have a gastro-enterostomy, he would feel safer with an anterior than a posterior one.

The complications of perforation and hemorrhage in gastrojejunal ulcer have already been mentioned but there remains to discuss the most serious, the most distressing, and from the point of view of management, the most perplexing of all the complications associated with this condition, that is, the perforation of the anastomatic marginal ulcer into the transverse colon producing a gastrojejunocolic fistula.

The mechanism of the production of a gastrojejunocolic fistula is first the occurrence of a gastrojejunal ulcer at a gastro-enterostomy stoma. With these ulcers, there is usually associated a large area of inflammatory induration extending well out from the ulcer area into the root of the mesentery.

Gastrojejunocolic fistula occurs almost solely in posterior gastro-enterostomies. The posterior anastomosis of the jejunum to the stomach is often unwisely made through a

low opening in the posterior leaf of the gastrocolic omentum close to the transverse colon. This then results in the anastomosis resting close to, or in contact with, the transverse colon (a frequent technical error). The opening in the transverse mesocolon should be high (Fig. 3), thus keeping the anastomosed jejunum away from the transverse colon. The exudate from the gastrojejunal ulcer soon extends to the transverse colon, includes that structure in the inflammatory mass about the ulcer, and soon perforates into that structure. This complication is said to occur in about 11 per cent of the cases.

Gastrojejunocolic fistulas probably cannot occur except in patients who have had a gastrojejunal ulcer for some time. The condition is to be suspected in any patient who has had a gastro-enterostomy particularly for duodenal ulcer followed by a return of ulcer symptoms and with belching of gas with a fecal odor, with persisting diarrhea due to the dumping of undigested food through a large fistulous tract from the stomach into the transverse colon. This condition is to be suspected in such a patient also who in spite of a good food intake is progressively losing weight; likewise, due to the direct passage of food into the transverse colon from the stomach and so failure to be utilized.

We have seen gastrojejunocolic fistulas varying in size from that of a pencil point up to the size of a silver dollar, so that bismuth given by mouth passed rapidly into the colon and a bismuth enema passed quickly from the colon to fill the stomach. In proctoscoping a patient suspected of having a gastrojejunocolic fistula who had had tapioca for lunch, we have found tapioca in the rectum at four o'clock of the same afternoon.

The diagnosis of large gastrojejunocolic fistulas by X-ray as shown in Figure 2, is easily made. In small fistulas, however, the X-ray diagnosis can be made with considerably less certainty. The mechanism of the perforation of a jejunal ulcer into the colon is diagrammatically shown in Figure 4.

TREATMENT

There is a distinct conviction on the part of most persons dealing with ulcer that patients with gastrojejunal ulcers seldom respond satisfactorily and permanently to medical treatment, but in all cases medical treatment should be carried out to reduce acidity thus perhaps lessening the area of acute reaction about the ulcer and improving the general condition of the patient as an operative risk. In addition, we have a number of patients with undoubted gastrojejunal ulcer who have been able to get along satisfactorily for a number of years on medical treatment.

Since any patient who has developed a gastrojejunal ulcer has demonstrated that he falls in the group of patients who are particularly liable to recurrent ulcer, it is the feeling of many surgeons and it is our conviction that any surgical measure short of radical subtotal gastrectomy will be likely to be followed by a recurrent ulcer and, as shown in figures from the literature, even with radical partial gastrectomy recurrent gastrojejunal ulcer will still occur in a small percentage of cases. In defense of this position one must admit that the best operative procedure for such recurrent ulcers is the one which is followed by the most complete postoperative anacidity and that operation is undoubtedly subtotal gastrectomy. The mortality, however, in such an extensive operation as is necessary with gastrojejunal ulcers and on patients frequently in poor condition, is considerable, reported by one of its ardent advocates as 20 per cent and our mortality rate has been 15 per cent. On the other hand, it is claimed by many that the unhooking of the gastro-enterostomy and restoration of the digestive stream is frequently followed by a recurrence of the original ulcer and such has been our experience—40 per cent recurrent duodenal ulcer in such procedures.

There are certain basic facts which must be admitted in any discussion of the surgical treatment of peptic ulcer. It must be admitted that both physicians and patients have accepted and do accept the original peptic ulcer with all too great complacency. The mortality from hemorrhage alone in this group of patients while in our hands in the hospital has been 5 per cent, 1 in every 20 patients. It must be admitted that gastro-

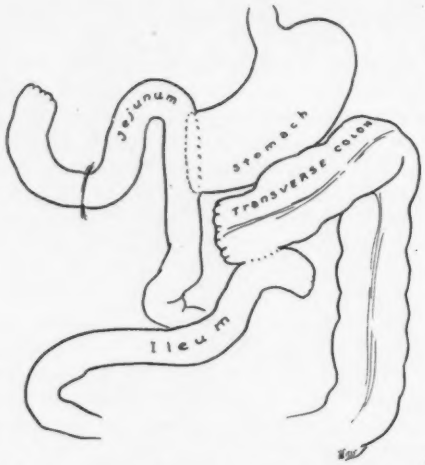


Fig. 6. This drawing diagrammatically illustrates the ideal procedure for gastrojejunocolic fistula: Resection of the stomach including the old gastro-enterostomy and the gastrojejunal ulcer, resection of the portion of the jejunum containing the ulcer, end-to-end anastomosis of the jejunum, resection of the ascending colon, hepatic flexure, and a portion of the transverse colon beyond the fistula into it, anastomosis of the jejunum to the cut end of the stomach and anastomosis of the ileum to the transverse colon. This, unfortunately, is too much surgery for many of the patients with gastrojejunocolic fistulas to endure. Up to the present it is, however, the only plan whereby one may remove the large gastro-jejunocolic fistulas without contamination of the peritoneum by colon contents. It must be understood that this discussion does not include the small gastrojejunocolic fistulas which can usually be handled quite satisfactorily by separation and inversion.

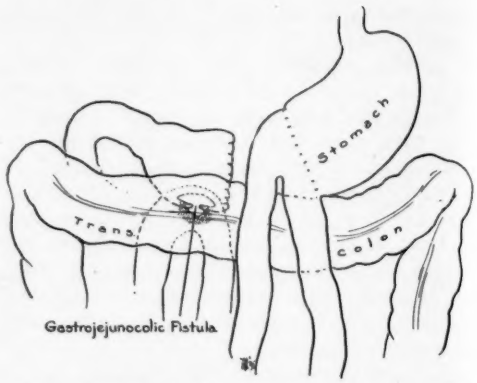


Fig. 7. This drawing illustrates the procedure described in the text which we have twice employed. Through a left rectus incision, the stomach is cut off proximal to the ulcerated stoma and fistula and the jejunum beyond the gastro-enterostomy anastomosed to the cut end of the stomach. In both of these cases operations were immediately successful but ultimately (26 days and 3 months) the patients died of conditions, one coronary disease and one untreated intestinal obstruction, not directly related to the procedure. This plan may still prove a useful procedure in dividing the radical removal of stomach, colon, and jejunum in the large gastrojejunocolic fistulas into a less shocking two stage procedure. It was hoped that by sidetracking gastric contents by this procedure, closure of the ulcer and lessening of the induration about the fistula might occur. Autopsy in both of these cases, in one 26 days after operation and the other 3 months after operation, showed the induration to be still marked and the ulcers unhealed. Should we employ this procedure again, we would, we believe, remove the lower end of the stomach, jejunum and right colon through a right rectus incision at the end of 3 weeks.

enterostomy is not a desirable type of operative procedure to be routinely applied to the surgical treatment of peptic ulcer as it has been in past years. It must be admitted that pyloroplasty (the safest of all operations for ulcer) is difficult to apply in many of the patients with duodenal ulcer due to the scarring and distortion of the duodenum by the ulcer. It must be admitted that radical partial gastrectomy gives the highest percentages of complete and permanent relief from ulcer symptoms and the lowest percentage of recurrent anastomatic ulcers, but it must also be frankly admitted that it has and probably always will have a mortality rate except in selected cases which both to the patient and surgeon is disturbing.

It must be admitted that while we can by operative procedures handle small gastrojejunocolic fistulas with reasonable satisfaction, we are faced with a situation which at least in our hands has up to the present proved almost insurmountable, when the fistulous opening into the transverse colon in gastrojejunocolic fistula is a large one, for example, the size of a quarter, half-dollar or dollar (Fig. 5) as it so often is.

In operating upon such large fistulas between the colon, stomach, and jejunum, one is faced with the dilemma of producing peritoneal contamination with colonic contents on separating the large fistula, with the need of trying to close a fistulous opening into the colon when that structure is badly indurated and so holds stitches badly, or with the necessity of doing a block removal of stomach, jejunum, and midcolon which necessitates three resections at one sitting, resection of the

stomach, jejunum, and transverse colon (Fig. 6). We have successfully accomplished this but it is a procedure of too great magnitude to be routinely applicable to this condition with a reasonable mortality. We have employed numerous procedures in an attempt to decrease the danger and mortality in these trying cases. Twice we have cut the stomach across proximal to the old anastomosis and so proximal to the gastrojejunocolic fistula, have closed the distal end and anastomosed a segment of jejunum by the Pólya method distal to the fistulous connection between the stomach, jejunum and colon. We have hoped by this procedure to cause the ingested food to pass directly into the jejunum beyond the old gastrojejunostomy and beyond the fistulous opening into the colon (Fig. 7), thus segregating the section of stomach and jejunum containing the ulcer and also segregating the fistula. By this plan it was hoped that food would be absorbed and utilized as it passed along the jejunum and not through the fistulous opening into the transverse colon, resulting as it has in some of the cases in a weight loss of several pounds a week.

Both patients made excellent operative recoveries but one died a cardiac death 26 days after operation when ready to go home and the other died of intestinal obstruction 6 months after leaving the hospital. We must admit that when we are faced with a patient with a gastrojejunal ulcer which has perforated into the transverse colon, and produced a gastrojejunocolic fistula of large caliber and surrounded, as they always are, by a large area of induration, see Figure 5, we are still considerably at a loss as to how it can be surgically cared for with reasonable safety.

We must admit finally, we think, and most importantly that most patients are not aware of how unsatisfactory the situation is as relates to the surgery of peptic ulcer and so do not feel as strongly as they should about the compelling need for modification of living, eating, smoking, and drinking habits, in order that they may avoid the necessity of facing an unsatisfactory surgical procedure or a satisfactory one with an unsatisfactory risk rate. One of us (FHL) is self-conscious of having harped upon this aspect of the ulcer situation, but nevertheless feels it his duty again to repeat that unless patients with a peptic ulcer are frankly told of this list of admissions and are not permitted to assume that the operation which they accept is an entirely satisfactory one, then how can they ever be made to take their responsibility seriously or finally as they all eventually must?

SUMMARY AND CONCLUSIONS

The literature has been reviewed from the date of the paper by the author and Dr. Jordan, 1928 to July, 1934. The number of reported anastomotic ulcers is recorded. The variation in percentages of anastomotic ulcer in gastro-enterostomy and resection is also recorded.

Excerpts from the writings of authors interested in this subject are quoted to show the wide range of opinions held by experienced surgeons regarding this subject both as relates to its origin and incidence.

As the result of this and our earlier (1928) review of the literature together with our experience, it is our conviction that gastroenterostomy is not an operation that should be routinely utilized for peptic, particularly duodenal, ulcer.

Some of the facts which predispose to the occurence of gastrojejunal ulcer are recorded.

A list of disturbing admissions regarding the surgery of peptic ulcer is frankly recorded. This is done with no purpose of being destructively critical but rather that they may be unhesitatingly faced and we again repeat that unless patients are freely told of these disturbing admissions, how can they ever be made to comprehend their responsibility seriously before or after operation, accept it finally, and live accordingly as they all eventually do in such other diseases as tuberculosis, pernicious anemia, and diabetes?

BIBLIOGRAPHY

1. ALLEN, N. M. Am. J. Surg., 1928, 5: 128; J. Michigan Med. Soc., 1931, 30: 496.
2. ANDREWS. Surg. Clin. N. America, 1933, 13: 1201.
3. BAGER, B. Acta. chirurg. Scand., 1929, 64: Suppl. 11.
4. BALFOUR, D. C. Ann. Surg. 1928, 88: 548; Ann. Surg., 1929, 90: 535; Surg. Clin. N. America, 1929, 9: 23; Ann. Surg., 1930, 92, 558; Proceed. Mayo Clin., 1932, 7: 189.
5. BENEDICT, E. B. Surg. ,Gynec. & Obst., 1933, 56: 807.

6. Berg, A. A. Ann. Surg., 1930, 92: 340.
7. Bertrand, P. Lyon chir., 1932, 29: 577.
8. Bloch, L. J. Am. M. Ass., 1930, 95: 1883.
9. Braine, J. Bull. et Mém. Soc. nat. de chir., 1932, 58: 671.
10. Brandtner, C. E., and Bonnis, W. Deutsche Ztschr. f. Chir., 1932, 236: 93.
11. Bromley, L. Guy's Hospital Rep., 1930, 80: 227.
12. Broster. Brit. M. J., 1928, 2: 786.
13. Buckstein, J. Am. J. Roentgenol., 1932, 27: 59.
14. Budde, W. Arch. f. klin. Chir., 1928, 153: 600.
15. Cabot case. New England J. Med., 1929, 201: 783.
16. Camp, J. D. Med. Clin. N. America, 1930, 14: 767.
17. Caucci, A. Policlin., 1932, 39: 466.
18. Charrier. Arch. de mal. de l'appar. digest., 1931, 21: 1202.
19. Clavel, C. Rev. de chir., Par., 1933, 52: 207.
20. Davenport, C. B. J. Am. M. Ass., 1931, 97: 99.
21. Deaver, J. B. Atlantic M. J., 1928, 31: 798.
22. Douglas, J. Tr. Am. Surg. Ass., 1930, vol. 48.
23. Down, H. I. Proc. Staff Meet. Mayo Clin., 1931, 6: 205.
24. Ebeling, W. W. Ann. Surg., 1933, 97: 857.
25. Ehrlich, S. P. J. Am. M. Ass., 1928, 90: 1870.
26. Elansky, N. N. Arch. f. klin. Chir., 1930, 158: 113.
27. Estes, W. L., Jr. Ann. Surg., 1932, 96: 250.
28. Eusterman, G. B. Med. Clin. N. America, 1928, 11: 1371.
29. Finney, J. M. T., and Hanrahan, E. M., Jr. Ann. Surg., 1929, 90: 904.
30. Finsterer, H. Surg., Gynec. & Obst., 1931, 52: 1099.
31. Fischer, A. Zentralbl. f. Chir., 1932, 59: 790.
32. Fremont-Smith, M., and McIver, M. A. Am. J. M. Sc., 1929, 177: 33.
33. Friedman, J. G. Tr. Am. Surg. Ass., 1930, 48: 269.
34. Fromme, A. Beitr. z. klin. Chir., 1929, 147: 111.
35. Gatewood. Tr. Am. Surg. Ass., 1930, 48: 142.
36. Gosset, A. J. de chir., 1931, 38: 491.
37. Graham, Roscoe R. Gastrojejunal and jejunal ulcers. Not yet published. Read at last meeting of the American Medical Association.
38. Harberer, von H. Zentralbl. f. Chir., 1930, 57: 66.
39. Harper, F. R. Surg. Clin. N. America, 1933, 13: 843.
40. Hartwell, J. A., and Felter, R. K. Tr. Am. Surg. Ass., 1930, 48.
41. Hayon. Ann. Surg., 1930, 92: 602;(Paris Thesis,1929.)
42. Hinton, J. W. Surg. Clin. N. America, 1931, 11: 697.
43. Idem. Am. J. Surg., 1933, 20: 102.
44. Hinton, J. William, and Church, Reynold E. The incidence of gastrojejunal ulcer following gastroenterostomy. Am. J. Digest. Dis. & Nutrition, 1934, 1: 526.
45. Horsley, J. S. Tr. Am. Surg. Ass., 1930, 48: 133.
46. Hurst, A. F., and Cosin, C. F. Proc. Roy. Soc. Med., 1931, 24: 707.
47. Hurst, A. F., and Stewart, M. J. Lancet, 1928, 2: 742, 805.
48. Jones, T. E. Guy's Hosp. Rep., 1928, 78: 158.
49. Judine, S. Bull. et mém. Soc. nat. de chir., 1929, 55: 1233.
50. Idem. J. de chir., 1931, 38: 2.
51. Just, E. Wien. klin. Wchnschr., 1929, 42: 500.
52. Kiefer, E. D. Surg. Clin. N. America, 1932, 12: 687.
53. Klein. Ann. Surg., 1929, 90: 65.
54. Konjetzny, G. E. Ergebn. d. inn. Med. u. Kinderh., 1930, 37: 184.
55. Lamson, O. F. Surg. Clin. N. America, 1933, 13: 95.
56. LePlat. Bull. et mém. Soc. de chir. de Par., 1928, 20: 666.
57. Leriche, R. Bull. et mém. Soc. nat. de chir., 1929, 55: 558.
58. Lerman, J., Pierce, F. D., and Brogan, A. J. J. Clin. Invest., 1932, 11: 155.
59. Lewisohn, R. Ann. Surg., 1930, 91: 520.
60. Lindau, A., and Wolff. Surg., Gynec. & Obst., 1931, 53: 621.
61. Louria, H. W. Surg., Gynec. & Obst., 1928, 47: 493.
62. Luff, A. P. Brit. M. J., 1929, 2: 1074.
63. MacGuire. Ann. Surg., 1932, 95: 134.
64. Makkas, M. Beitr. z. klin. Chir., 1934, 159: 61.
65. Mallet, Guy P. Lyon méd., 1933, 151: 193.
66. Martin, E. Lyon chir., 1933, 30: 641.
67. Meyer, K. A., and Rosi, P. A. Surg. Clin. N. America, 1933, 13: 1251.
68. Miller, J. R., and Holmes, W. H. Illinois M. J., 1933, 64: 487.
69. Morton, C. B., and Graham, J. B. Ann. Surg., 1930, 91: 73.
70. Moynihan, B. Brit. M. J., 1928, 2: 1021.
71. Neller, K. Deutsche Ztschr. f. Chir., 1930, 222: 165.
72. Nixon, P. I., and Lowry, S. T. Med. J. & Rec., 1928, 128: 584.
73. Nystrom, G., and Soderberg, F. Zentralbl. f. Chir., 1928, 55: 258.
74. Nystrom, G. Tr. Am. Surg. Ass., 1930, 48: 162.
75. Oberniedermayr, A., and Stahnke, E. Deutsche Ztschr. f. Chir., 1929, 214: 387.
76. Owings, Smith. Proc. Soc. Exper. Biol. & Med., 1932, 29: 832.
77. Porzelt, W. Zentralbl. f. Chir., 1928, 55: 1740.
78. Ramb, H. Deutsche Ztschr. f. Chir., 1933, 240: 20.
79. Robinson, V. P. Lancet, 1928, 1: 703.
80. Saunders, E. W. Ann. Surg., 1930, 91: 2.
81. Schwarz, E. Therap. d. Gegenw., 1928, 69: 157.
82. Idem. Arch. f. klin. Chir., 1928, 151: 445.
83. Schwarz, F. Beitr. z. klin. chir., 1929, 147: 116.
84. Scott, W. J. M. Arch. Surg., 1929, 18: 1584.
85. Simon. Paris chir., 1929, 1007.
86. Sole, R. Semana méd., 1929, 2: 776.
87. Starlinger, F. Wien. klin. Wchnschr., 1929, 11: 905; Arch. f. klin. Chir., 1930, 162: 564; Ergebn. d. Chir. u. Orthop., 1932, 25: 380.
88. Steden, E. Deutsche Ztschr. f. Chir., 1931, 230: 404.
89. Steinberg, M. E. Am. J. Surg., 1934, 23: 137.
90. Strode, J. E. Am. J. Surg., 1933, 21: 240.
91. St. John, F. B. Ann. Surg., 1930, 92: 597.
92. Strauss, A. A. J. Am. M. Ass., 1928, 90: 181.
93. Thompson, W., and Stewart, M. J. Brit. J. Surg., 1928, 15: 517.
94. Urrutia. Z. Org. Chir., 1929, 43.
95. Valdoni. Policlin., 1932, 39: 444.
96. Viviani, R. Bull. d. sc. med., Bologna, 1931, 103: 81.
97. Walton, A. J. Textbook of Surgical Dyspepsias, 1930; Brit. J. Surg., 1934, 22: 33.
98. Walzel, P. Zentralbl. f. Chir., 1931, 58: 2679.
99. Weir, J. F. Am. J. Surg., 1929, 7: 505.
100. Wilkie, D. P. D. Ann. Surg., 1934, 99: 401.
101. Willis, P. W. Surg. Clin. N. America, 1933, 13: 1531.
102. Woodside, C. J. A. Brit. M. J., 1931, 1: 667.
103. Zukschwerdt, L., and Eck, T. Deutsche Ztschr. f. Chir., 1931, 232: 299.

TREATMENT OF ACUTE FATAL HEMORRHAGE BY INJECTION OF ARTIFICIAL BLOOD SUBSTITUTES[1]

A Comparative Study of Artificial Blood Substitutes

Dr. A. W. J. H. HOITINK, Utrecht, Holland
From the Laboratory for Physiological Chemistry, Prof. Dr. W. E. Ringer, Director; and the Institute for Pathology, Prof. Dr. R. de Josselin de Jong, Director, University of Utrecht

ONE would seem to be behind the times if today he attempted to save an exsanguinated patient by some means other than by blood transfusion. If we study the literature on blood transfusion, it is apparent that in numerous cases blood transfusion has saved life after great hemorrhage.

It is true, however, that this operation may not be entirely without danger, for often there may be injurious consequences, sometimes even death.

It is not surprising that these disagreeable experiences with blood transfusion occur; for in performing a blood transfusion operation, we inflict a very complicated system, the blood of the donor, upon another equally complicated system, the blood of the recipient, and these two systems possess a certain degree of individuality.

Blood testing to determine types and quality of blood at best gives only an imperfect idea of the real properties of the bloods which are to be mixed. If one reflects a moment about the numerous known, but more especially the unknown, properties of blood in their infinitely changing individual characteristics blood transfusion at present can only be called a "dark" operation, as we do not know exactly what is put into the blood circulation of the recipient and what will be the consequences. This is a great disadvantage and justifies the seeking for other means of treating acute fatal hemorrhage.

For about 50 years infusion was considered the method of choice in the treatment of great losses of blood; artificially prepared fluids (artificial blood substitutes) were infused or injected in an effort to avert fatal consequences in great blood loss. At first sodium chloride solution was the principal solution used. Gradually, however, it was supplanted by other fluids which were expected to give better reactions[2]. Treatment by infusion was thrown into the background, however, when the introduction of the blood of donor to recipient was considered to be the only right method to use. As the use of blood transfusion has become more extensive, difficulties have been encountered and as there are still obstacles to overcome the investigation of the other methods of treating considerable blood loss should be continued.

EXPERIMENTAL DATA

Therefore, I began the study of artificial blood substitutes, the injection of which—if they proved to be valuable in an acute hemorrhage—would as a rule have in addition the advantage of surpassing blood transfusion in so far as the treatment might be more quickly accomplished.

The life saving actions of several artificial blood substitutes were compared. For this purpose a large quantity of blood was taken from dogs by allowing the blood to flow from the carotid artery through a cannula, and shortly afterward injecting the substitute into the external jugular vein. The immediate reaction was determined as well as the late recovery of the animal. Much attention was paid to the question as to how far the bleeding should be carried in order to determine the comparative values of the substitutes as to their life saving actions. It seems to me that the methods generally used to obtain equal losses of blood are inadequate; I believe that we must determine rather what effect the loss of a certain amount of blood will have on the animal in question.

Judgment as to the seriousness of a hemorrhage must be based on the reaction of the animal to the loss of blood; from the symptoms

[2] See the extensive: "Historical review of the development of substitution of blood by means of artificial substitutes," in my thesis, pp. 175 to 235.

[1] The results of my research were extensively described in my book entitled "Zyn er'kunstmatige sera' met een byzonder gunstige werking by bloedverlies? Vergelykend onderzoek over de werking van verschillende kunstmatige bloedvervangmiddelen by levensgevaarlyke bloedverliezen." Thesis de doct., Utrecht, Holland, Feb., 1934.

which the animal itself shows during the increasing loss of blood we must try to ascertain the degrees of artificial anemia in their biological significance as applied to the animal in question.

My study of the action of blood substitutes has proved that we must stop bleeding the animal at an accurately determined moment at which: (a) the loss of blood would certainly prove fatal without the infusion; (b) the anemia has an equivalent "biological value" in each separate animal used.

I found that to determine this moment attention must be directed especially to: (1) the symptoms shown by breathing; (2) the peculiarities of the pulse—"tactile" observation on the femoral artery, and "visual pulse control" by observing the stream of blood flowing from the artery; (3) the appearance of convulsions.

Observation of respiration revealed four forms of breathing as the loss of blood increased—approximately the same as those described by E. Holovtschiner for rabbits in similar circumstances.

The convulsions noticed are, first, extensor spasms of the paws, the presence of which proved to be of no practical value in estimating the grade of artificial anemia. Besides, "general extensor convulsions" were observed, by which is meant tonic spasms of the whole animal. During such spasms the paws are tensely stretched, the head and neck are extended far backward, and the back is bent in opisthotonus. It is this "general extensor spasm" which is of great importance in determining the moment at which the hemorrhage must be stopped.

By paying attention to each of the aforesaid symptoms separately, however, it appeared to be impossible to determine sufficiently accurately the moment at which the loss of blood should cease, if the two demands mentioned were to be complied with. However, by experiments, a complex of symptoms was evolved by observing, as a whole, the convulsions, the respiration, and the peculiarities of the stream of blood together.

It appeared that the three symptoms to be mentioned, each one of which by itself may be an important indicator of the degree of anemia, show themselves almost simultaneously as in a "snapshot," the general spasm being the one to produce the effect of suddenness. The moment at which these symptoms show themselves in their peculiar composition, can be accurately determined, and is thus of practical use in pointing out when the bleeding should be stopped. The three symptoms are (a) the sudden appearance of a *general* extensor spasm, extensor convulsions of the paws having been noticed before at different periods; (b) the sudden stopping of flow or dripping of blood for a moment, to continue again or else to stop entirely; (c) the end of the syncope form of breathing, that is, the animal breathes only superficially and very irregularly; only a few breaths are taken, or the respiration ceases altogether.

From the curious coincidence of these three important symptoms, I thought I could draw the conclusion that the loss of blood had passed a certain threshold determined by the animal itself and had attained "critical proportions." I could demonstrate that such a loss of blood was fatal for the animal.

By continually increasing the bleeding until there is visible the "triad of symptoms of functional fatal hemorrhage," which may be accurately observed, it was possible in several animals, to cause fatal hemorrhages all of which are biologically equivalent.[1]

It was now possible to compare with sufficient accuracy the action of different substitutes for blood when given to different animals.

The characteristic symptoms of "functional fatal hemorrhage" appeared when on an average 56 to 57 cubic centimeters of blood per kilogram of body weight had been lost. The smallest loss of blood at which the symptoms appeared was 50 cubic centimeters and the largest 64 cubic centimeters per kilogram of body weight.

Hemorrhage, which is continued until marked irregular syncope respiration is seen, is also considered fatal for dogs. Though experiments in which the animals have been bled to this extent cannot be included when

[1]By "functional fatal hemorrhage" I mean that so much damage has been done to the animal organism through the loss of blood that its functions are very greatly hampered, while "mechanical fatal hemorrhage" simply means that no more blood can be extracted from the animal.

TABLE I.—BLEEDING AND SUBSEQUENT INJECTION OF SODIUM CHLORIDE SOLUTION INTO THE VENA JUGULARIS EXTERNA

Dog number	Sex, age	Weight, kilograms	Loss of blood c. cm.	Loss of blood per kilogram of body weight c. cm.	Triad?	Quantity of substitute injected	Result of the injection	Anesthesia
11	♂ ±5y	21.5	1200	56	No	960 c. cm. 0.7% Na-Cl solution	Saved	Local
16	♀ ±2y	16.5	1050	64	Yes	840 c. cm. 0.9% Na-Cl solution	Saved	Local*
19	♀ 9à10y	23	1200	52	Yes	960 c. cm. 0.9% Na-Cl solution	Saved	Local
29	♂ ±5y	14.5	800	55	...	640 c. cm. 0.9% Na-Cl solution	Saved	Local†
24	♀ ±3y	17.5	1100	63	Yes	860 c. cm. 0.9% Na-Cl solution	Saved	Local
27	♂ ±6y	27	1200	44	No	960 c. cm. 0.9% Na-Cl solution‡	Saved	540 m. gr. morphia‡ subcutaneous

*Makes the impression after the bleeding of being dead.
†Bleeding was probably extended beyond the appearance of the "triad." This dog had diseased kidneys before the operation.
‡About 6 weeks before this dog suffered a hemorrhage of 55 c. cm. per kilogram of body weight, after which "chlorides-Normet" were injected with good result.

comparing the substitutes for blood, they can give us information as to the latter's power to save life.

In accordance with the principles outlined, I examined in acute fatal hemorrhage, the action of sodium chloride solution 0.7 and 0.9 per cent; Ringer's fluid[1] (0.95 per cent NaCl, 0.02 per cent KCl, 0.02 per cent $CaCl_2$); Locke-Ringer (0.9 per cent NaCl, 0.024 per cent $CaCl_2$, 0.042 per cent KCl, 0.1 per cent glucose, 0.02 per cent $NaHCO_3$, saturated with oxygen); Tyrode (0.8 per cent NaCl, 0.02 per cent KCl, 0.02 per cent $CaCl_2$, 0.01 per cent $MgCl_2$, 0.005 per cent NaH_2PO_4, 0.1 per cent $NaHCO_3$, 0.1 per cent glucose); normosal, tutofusin (these two fluids are modern substitutes, prepared in a factory; the composition is kept a secret, but is very much like Tyrode's fluid); and sérum Normet chirurgical.

Sérum Normet is a citrate solution, used by L. Normet[2] and is based on his investigations on the therapeutic activity of citrates. Normet's solution consists of 22 grams of sodium citrate, 6.50 grams of neutral calcium citrate, 4.50 grams of neutral magnesium citrate, 1 gram of iron ammonium citrate, 0.15 gram of manganese citrate, distilled water to 1000 cubic centimeters. Twenty cubic centimeters of this solution are added to 1000 cubic centimeters of sodium chloride solution 0.7 per cent. The liquid thus obtained can be used as a blood substitute and for that purpose is injected into the circulation up to the equivalent of two-thirds to four-fifths of the amount of blood lost.

Normet claimed that the citrate solution he used as a blood substitute not only had a better immediate action, but also a peculiar, stimulating influence on the restoration of the blood. The favorable action which Normet claimed for the sérum Normet he ascribed to the fact that the metals in the fluid were present as citrates.

In order to determine whether a possibly more favorable action of the sérum Normet in acute profuse hemorrhages is due to the fact that the metals used are combined with citric acid, I made a solution that contained the metals in the sérum Normet but used chlorides in equivalent quantities (chlorides Normet). A comparison was made of the effects of sérum Normet and chlorides Normet.

Water was also once injected.

The results of my experiments on the life saving action of the various substitutes are given in Tables I to IV.

As it was only later on in our study that a clear cut image of the symptoms of fatal hemorrhage was formed, these symptoms were not noticed in a number of dogs in the early experiments. The greater number of the animals, however, suffered a fatal loss of blood, so that conclusions can be reached as to the life saving action of the fluid in question. For a comparison of the value of the various infusion liquids we can make use

[1] The methods of preparing the different fluids are mentioned in full in my thesis.
[2] A. W. J. H Hoitink, thesis, pages 226–234, contains a summary of Normet's work and of the literature on his fluids.

TABLE II.—BLEEDING AND SUBSEQUENT INJECTION INTO THE VENA JUGULARIS EXTERNA OF MORE COMPLICATED SOLUTIONS, VIZ., RINGER'S FLUID, LOCKE-RINGER AND TYRODE SOLUTIONS; NORMOSAL AND TUTOFUSIN

Dog number	Sex, age	Weight, kilograms	Loss of blood, c. cm.	Loss of blood per kilogram of body weight, c. cm.	Triad?	Quantity of substitute injected	Result of the injection	Anesthesia
3	♀ ±6y	20.3	1100	54	No	920 c. cm. of Ringer's fluid	died 7 hours after injection	480 m. gr. of morphia subcutaneous, completed by ether narcosis
7	♀ ±2y	16	740	46	No	625 c. cm. of Locke-Ringer's fluid	Saved	Local*
6	♀ 1½y	15	710	47	No	600 c. cm. Locke-Ringer	Saved	Local*
18	♂ 6y	16	940	59	Yes	750 c. cm. Tyrode	Saved	Local†
15	♂ 3à4y	25.8	1440	56	Yes	1150 c. cm. Normosal	Saved	Local‡
31	♀ ±4y	28.5	1120	39	bleeding extended beyond triad	880 c. cm. Tutofusin	Dead	Local§

*Doubtful if this loss of blood is certainly fatal.
†Makes the impression after the bleeding of being dead.
‡First days after operation in poor condition.
§Anemic dog, in which the "triad" showed itself after comparatively slight loss of blood.

TABLE III.—BLEEDING AND SUBSEQUENT INJECTION OF "SÉRUM NORMET CHIRURGICAL" INTO THE VENA JUGULARIS EXTERNA

Dog number	Sex, age	Weight, kilograms	Loss of blood, c. cm.	Loss of blood per kilogram of body weight, c. cm.	Triad?	Quantity of substitute injected, c. cm.	Result of the injection	Anesthesia
1	♂ ±7y	20.2	850	42	No	775	Saved	Local*
2	♂ ±7y	24.2	1100	45	No	825	Saved	550 m. gr. of morphia subcutaneous
4	♂ ±2y	19.75	850	43	No	675	Saved	400 m. gr. of morphia subcutaneous
5	♂ ±4y	27	1450	54	No	1120	Saved	Local; completed by ether narcosis
13	♂ 1½y	20	1000	55	No	800	Saved	Local
14	♂ ±3½y	21.9	1100	50	No	880	Saved	Local
17	♀ ±2y	18.5	1080	58	Yes	875	Saved	Local†
20	♂ 4à5y	24	1200	50	Yes	960	Saved	Local‡
30	♂ ±6y	29.5	1850	63	Yes	1480	Saved	Local§

*Doubtful if this loss of blood is certainly fatal. Spleen was removed some months before.
†In bad condition directly after operation.
‡First days after operation less good (abnormalities in urine).
§This dog had diseased kidneys before the operation.

only of the experiments in which the bleeding was stopped as soon as the "triad" made its appearance. Such experiments are indicated in the tables.[1]

In surveying the results of our study it was found that all substitutes had the ability to save life after biologically equivalent fatal hemorrhages. It is not surprising that the dog that received an injection of Ringer solution died (Table II), if attention is drawn to a few details. After general anesthesia by means of a heavy dose of morphine supplemented with ether narcosis, this dog was fatally bled. In addition to these two factors harmful to recovery after hemorrhage, the pathologist found at postmortem examination that the dog had been suffering from cancer. Moreover peculiar tumors were found in the spleen (multiple splenofolliculomas). In the

[1] The dog which, after a loss of blood of 1150 cubic centimeters (50 cubic centimeters per kilogram of body weight) received an injection of 920 cubic centimeters of sterile distilled water into the vena jugularis externa, died about 1 minute after the injection.

TABLE IV.—BLEEDING AND SUBSEQUENT INJECTION OF "CHLORIDES NORMET" INTO THE VENA JUGULARIS EXTERNA

Dog number	Sex, age	Weight, kilograms	Loss of blood, c. cm.	Loss of blood per kilogram of body weight, c. cm.	Triad?	Quantity of substitute injected, c. cm.	Result of the injection	Anesthesia
23	♂ 4½y	25	1375	55	Yes	1100	Saved	Local*
27	♂ ±6y	24.5	1350	55	Yes	1080	Saved	Local†

*After operation this dog got diseased kidneys; urine also showed reduction. (Makes the impression after the bleeding of being dead.)
†After operation a few abnormalities in urine, also reduction.

tumors and the surrounding tissue much blood was found; at a distance from the tumors the splenic tissue was conspicuously poor in blood. Therefore, I wondered if the spleen had been able to react sufficiently to offset the loss of blood, as described by J. Barcroft. It seemed to me quite possible that this diseased spleen in addition to an insufficient power to swell, i.e., to stock blood, had been able to contract only imperfectly, so that the organism lacked an important means of defense against the consequences of acute loss of blood. If these factors all acting unfavorably are considered I think that the death of this dog should not be attributed to Ringer's solution.

The experiment in which tutofusin was injected does not give an idea as to the life saving action of this substitute, as the infusion was administered to an anemic dog and the bleeding was continued far beyond the appearance of the "triad."

If the fact that water is by no means harmless to the blood is considered, the result of the experiment with water is not astonishing; for in addition to the fatal loss of blood further damage was done by the destruction of a great number of the remaining blood cells, when a large quantity of water was so quickly injected into the blood.

Apart from these cases in which it is quite obvious that infusion could not save life, all substitutes for blood injected appeared to be life saving. That the more complicated substitutes produced better results than sodium chloride solution I could find no proof; on the contrary, ordinary sodium chloride solution was unsurpassed in saving the animals doomed to death by loss of blood.

As a rule the dogs recovered quickly after the injection of the various substitutes. The defective respiration, which sometimes stopped entirely, showed quick improvement. Then there was a peculiar form of respiration characterized by a short, scarcely audible inspiration, followed by longer snuffling expiration. The sound thus produced reminded one of the noise made by a railway engine as it begins to move. I called this form of breathing the "engine respiration." It is especially remarkable that the expiration is predominant. It seems as if the organism uses this form of breathing to rid itself of injurious substances. After a short time the "engine respiration" changes again into usual breathing without an abnormal predominance in expiration. All other signs of returning life quickly appear after the infusion.

No real damage due to the infusion of substitutes was noticed except that in a few instances there were abnormalities in the urine for a short period[1] especially after infusion of chlorides Normet and sometimes after sérum Normet. These abnormalities in the urine were not of a serious nature, however. In dogs which had distinctly diseased kidneys, no bad effect as far as the urine was concerned was observed after the injection of a 0.9 per cent sodium chloride solution and of sérum Normet after hemorrhage.

In addition to the study of the life saving action of artificial blood substitutes, the following determinations as to the influence of the substitutes on the restoration of the blood were made: the number of erythrocytes per cubic millimeter; the hemoglobin percentage, the method of S. Y. Wong being used; the Sahli value; the average amount of hemoglobin of an erythrocyte; the number of reticulocytes, polychromatophilic erythrocytes,

[1] After hemorrhages without subsequent infusion we also find abnormalities in the urine of dogs, as is shown by this research and another we have taken in hand.

TABLE V

Injected fluid	Number of reticulocytes before operation	Greatest number of reticulocytes after operation	Days after operation greatest number was observed	Loss of blood per kilogram of body weight c. cm.
Sodium chloride solution	3, 4	44, 5	6	52
Sodium chloride solution	2, 3	37, 1	6	55
Sodium chloride solution	1, 9	26, 2	6	63
Locke-Ringer	4	10 (and 16)	10 (and 39)	46
Tyrode	2, 2	31, 6	6	59
Normosal	3	25	7	56
Sérum Normet	4	24	7	43
Sérum Normet	3	30	6	54
Sérum Normet	4, 1	28, 6	4	50
Sérum Normet	7	48	7	50
Sérum Normet	3, 5	26, 8	6	63
Chlorides Normet	2, 2	28, 2	6	55
Chlorides Normet	4, 5	17, 2 and 17, 5	3 and 8	55
Bleeding without subsequent infusion	2, 8	10, 4	8	31

normoblasts, red blood cells with Howell-Jolly particles and other nucleus particles, basophilic erythrocytes; form and size of the red blood cells; other peculiarities of the red blood picture; the number of leucocytes per cubic millimeter; the relative number of the different sorts of leucocytes. Subsequently we examined the total proteins of the blood plasma, the albumin and globulin content, the relative proportion of the albumins and globulins, the non-protein nitrogen content of the plasma. We tried especially to determine the magnitude of the restorative power of the solutions by comparing the number of reticulocytes before the hemorrhage and after the injection of the solution.

Table V gives an idea of the behavior of the reticulocytes after hemorrhage and subsequent injection of the various blood substitutes used by me.

If we assume that a comparison of the number of reticulocytes per 1000 erythrocytes present during the restoration of the blood with the number before the hemorrhage is an indication of the magnitude of the restoration of the blood, then my experiment would indicate that the sérum Normet did not have a distinct stimulating action on the hematopoietic organs. It goes without saying that here again the unknown peculiar restorative power of the animal in question makes an accurate comparison impossible. We may, therefore, only venture an opinion as to the more or less favorable action of the substitutes used on the restoration of the blood, as evidenced by the distinct differences in the number of reticulocytes. From the results shown in Table V, it does not seem that a more favorable result is secured with sérum Normet than with salt solution in restoring the blood. If we compare the number of reticulocytes before operation with the greatest number after the operation, it is remarkable to note that when salt solution was used the largest number on an average was 14 times the normal number, whereas in the experiments in which sérum Normet was injected, the number on an average was only 8 times the normal.[1] These facts seem to speak rather in favor of the sodium chloride solution.

Not one of the substitutes used, however, showed an extraordinarily favorable influence on the restoration of the form elements, hemoglobin and proteins. No evidence was found to indicate a stimulating effect of the sérum Normet on the hematopoietic organs.

In addition to these investigations, we made tests to determine how rapidly the urine and the sodium chloride were excreted after great loss of blood and subsequent infusion. These experiments showed that the organism which has lost most of its blood retains for some time the substitutes injected. I did not find any evidence of a quick excretion of the substitutes; this is especially true of the sodium chloride solution. I did find, however, that after infusion of a sodium chloride solution in a dog that had lost no blood, an increased secretion of urine and sodium chloride started soon after the infusion.

Summarizing, it appeared from my experiments that the artificial substitutes for blood injected into a vein after an acute profuse hemorrhage save life. A comparison of the merits of salt solution and other more compli-

[1] For this comparison with the Normet experiments only the results were used in which the loss of blood was about as large as in the saline solution experiments.

cated manufactured substitutes showed that the latter brought about no more favorable action than the ordinary sodium chloride solution.

Though we did not find any damage, even at autopsy, when a 0.7 per cent sodium chloride solution was used, a 0.9 per cent solution is preferable, as evidenced by the experiments of H. J. Hamburger.

DISCUSSION OF SEVERAL BLOOD SUBSTITUTES

With my results as a basis and after an extensive study of the literature on the infusion liquids, I have attempted to criticize the artificial blood substitutes as to their worth in acute fatal hemorrhage. Some of the solutions most commonly used will be discussed briefly (17).

1. Physiologically equilibrated solutions. As appears from my experiments these solutions show no better effect than the 0.9 per cent solution of sodium chloride. One great disadvantage in using the more complicated solutions is that it is very difficult to prepare them in a perfectly sterile manner without damaging their composition. In the modern preparation made in factories—normosal, tutofusin —this difficulty was not removed. Here we refer to A. Beck and also to W. Weichardt and H. Unger, who in 1928 and 1929 described the great dangers which may be attached to the injection of these liquids as a result of their not being quite sterile.

2. Colloid infusion fluids. Best known is W. M. Bayliss' (5) solution consisting of 7 per cent gum arabic, dissolved in 0.9 per cent sodium chloride solution. The addition was said to keep the liquid in the blood vessels, for it was thought that the non-colloid liquids after infusion into the circulation disappeared from it very quickly. But this is by no means certain. The so called dilution tests, by which certain elements in the blood are estimated before and after infusion, are valueless as far as determining the amount of infusion fluid circulating in the blood stream. It is especially from the varying number of erythrocytes per cubic millimeter that calculation is made as to the rapidity with which the injected fluids disappear from the circulation. However, six factors are to be kept in mind in estimating the number of erythrocytes per cubic millimeter after hemorrhage and subsequent infusion, viz.: (a) the quantity of blood remaining in the circulation; (b) the quantity of infusion fluid still in the blood vessels; (c) the tissue fluid which flows into the circulation; (d) the quantity of blood which proceeds from the spleen and which has a different composition to that already in the circulation; (e) the blood which is recruited from other blood stores; (f) the number of red blood cells damaged by the injection.

To draw a conclusion from the number of red blood cells per cubic millimeter as to the disappearance of the injected fluid from the circulation (which is, after all, only one of the many processes which take place) seems to me to be entirely arbitrary and not permissible. These same scruples exist when trying to obtain an impression of the rate of disappearance of the fluids by calculating the rise or fall of the hemoglobin or of the protein content of the plasma. If we use the proteins as an indicator, we must take the possibility into consideration that the walls of the blood vessels may be permeable for these substances in both directions. Also in determining the hematocrit—which is an unreliable method itself—the factors mentioned exercise their influence.

Moreover, the hemoglobin content did not always rise or fall with the number of red blood cells per cubic millimeter. The man who makes use of the erythrocyte count must get other results from his "dilution tests" than he who uses the hemoglobin content.

The colloid infusion fluids have no more favorable action than the fluids I used in my experiments. Barthélémy (5), by means of the Bayliss gum salt solution, could save dogs from which 60 to 70 per cent of the blood had been taken. If the hemorrhage was extended farther, the solution proved to be ineffective in saving life. The loss of blood in the experiments of Barthélémy was about as great as those in my dogs and the animals were saved by non-colloid fluids. I must also mention that the literature repeatedly describes dangers which may follow the injection of gum salt solutions. The *Journal of the American*

Medical Association (12) even warned against the gum salt solutions in an editorial.

At the end of this article I shall call attention to a theoretically construed disadvantage of the colloid fluid.

3. *Sérum Normet.* On the basis of our tests we could not discover any particularly favorable action of sérum Normet over sodium chloride solution. Moreover as J. Giraud and P. Silhol (13), and E. Bressot (11) observed dangerous complications after the injection of this fluid—one of my observations also tends in this direction (16)—the use of sérum Normet cannot be recommended.

4. *Isotonic sugar solutions.* As far as I can learn, isotonic sugar solutions, as blood substitutes, have never been proved to give better results than sodium chloride solutions. I believe that they have one disadvantage and that is that especially if they are kept in stock for some time the chance of alterations in the composition is greater. Then, too, it does not seem to me to be good practice to inject sugar into the circulation in the usual quantities, for a very unnatural hyperglycemia is caused, which certainly has its disadvantages.

By making the infusion liquid isotonic by means of sodium chloride, a solution is formed which is more "akin" to blood.

5. *Hypertonic (sugar) solutions.* Especially E. Simenauer tried to draw the tissue fluid to the vessels by injecting a small quantity of a hypertonic glucose solution into the circulation (40 per cent invert sugar solution, known as "shock calorose," of which 30 cubic centimeters is to be injected). This method of treatment does not seem to me quite the right one in acute heavy hemorrhage. An attempt is made to draw the tissue fluid more quickly to the vessels, but the injection into the vessels of the necessary fluid acts more quickly and better answers the purpose. Besides, the dehydration of tissues of the whole body is thus overcome.

6. *Blood transfusion.* In my experiments, in which the bleeding was as extensive as possible, I was quite successful in substituting for the lost blood liquids that did not contain red blood cells or blood serum. It is apparent that it is not necessary to infuse strange blood in acute dangerous hemorrhages. I would point out again that the great dangers connected with blood transfusion have influenced me in the conclusion that the prevailing opinion that hemorrhage calls for transfusion, broadly speaking, is not right.

7. *Sodium chloride solution.* On the basis of my own experiments, complemented by the facts found in the literature, I have come to the conclusion that in acute fatal hemorrhages the injection into a vein of 0.9 per cent sodium chloride solution is preferable to the injection of the other artificial blood substitutes and to blood transfusion[1]. The objections to sodium chloride solution I have discussed in my thesis and I have tried to confute them.

My opinion is that for medical practice the 0.9 per cent sodium chloride solution is a blood substitute which can be prepared at any place and at any moment, is easily administered, and has an excellent action. Elsewhere I have tried to explain the advantages of sodium chloride solution theoretically (16). I shall summarize very briefly.

1. In the treatment of acute dangerous hemorrhage the most urgent demand is a quick replenishing of the fluid of the vessels, so that the circulation can continue (F. Goltz) and the organism striving for recovery is helped past a dead-lock.

2. The various substitutes act, as to the propulsion of the contents of the vessels, in accordance with their volume. The water, which all infusion fluids have in common, and which gives them volume, stamps them as good substitutes. Mere water cannot be used for the injection into the circulation. However, if water is rendered tolerable to the body by adding sodium chloride to it, it is an excellent blood substitute. Of the other additions no particular, favorable action is seen in the infusion experiments. We have already pointed out that there are practical disadvantages.

3. The "unphysiological fluid" injected into the blood (e.g., sodium chloride solution) is

[1]As to chronic loss of blood and the non-staunched acute hemorrhages, on the basis of the research no definite method of treatment can be indicated as the best. However, I draw attention to the observations of F. J. Bosc, V. Vedel, Weisz, Widal, and Chantemesse. They thought that they noticed a contracting of the blood vessels after infusion of sodium chloride solution by which staunching of blood was said to be effected. If these observations are correct, the injection of sodium chloride solution can also be of service in non-staunched (acute) hemorrhages.

turned into a more physiological one after some time. For not only do we inject the substitute into the circulation itself but we introduce it into the whole quantity of fluid the body possesses because a constant exchange is taking place between the different fluids until the physiological margin is reached. That the organism with its large store of "physiological" fluid is easily able to neutralize the slight change into an "unphysiological" direction, is proved by the good results of the numerous (sodium chloride) infusions.

4. We put the least possible obstacles in the way of this turning of the fluid in the circulation to a physiological solution if we administer as a blood substitute water that is rendered harmless in the most simple way by the addition of sodium chloride. I consider the fact that it is easily movable an advantage. The great mobility of the liquid is a better guarantee of the quick issue of exchange that takes place to accomplish the "physiological balance" in regard to the composition of the fluid in the entire body. Therefore it seems to me biologically incorrect to use great effort to retain all the fluid injected in the circulation, as for instance when colloid infusion liquids are used. The loss of fluid suffered by the whole organism after a great hemorrhage is also fought more efficaciously by "movable" infusion liquids.

5. In acute dangerous hemorrhages the supply of blood from without the body is not necessary, sometimes dangerous.

Especially on these grounds I think I am able to support and to confirm the practical advantage of the 0.9 per cent sodium chloride solution.

As for the practical application of the 0.9 per cent sodium chloride solution, which we have given extensively elsewhere (17) we must remark that in acute fatal hemorrhage the solution should be injected *into a vein*, while the infusion of the sterile fluid which should be at blood temperature, should be carried out under some pressure in order to give an impetus to the insufficiently circulating blood.

As for the quantity of the fluid injected, if the infusion can be done soon after the hemorrhage, a smaller quantity of liquid may be used to see whether it is sufficient. In my experiments in which the quantity of blood lost was known, four-fifths of this quantity was injected in the form of artificial substitute. If a longer period has elapsed, as a rule an immediate injection of larger quantities of sodium chloride solution will be necessary.[1]

Lastly, the quantity of fluid to be injected should be determined by the result itself of the infusion. This principle should, of course, be applied with reason and judgment.

SUMMARY

Several artificial blood substitutes have been compared to determine their action in acute dangerous hemorrhages. For that purpose fatal hemorrhages which were biologically equivalent were produced in different dogs, to discover whether the dog's life could be saved by the injection of blood substitutes into the blood stream.

In addition, a study was made of the influence of the infusion fluids on the blood, and of the hemorrhage and subsequent infusion of substitutes on the urine and sodium chloride excretion.

It was found that none of the infusion liquids gave better results than the sodium chloride solution.

A search and study of the medical literature on the subject of the substitution for blood of artificial fluids were carried out, and the facts revealed by the author's own experiments were complemented by those reported in the literature. The author also gives his opinion as to the results of infusion after hemorrhage.

The conclusion is reached that the injection into a vein of 0.9 per cent sodium chloride solution after an acute dangerous hemorrhage is preferable to the use of other artificial substitutes and to blood transfusion.

Directions are given as to the method of sodium chloride solution injection.

REFERENCES

1. BARCROFT, J. Ergebn. d. Physiol., 1926, 25: 818–861.
2. BAYLISS, W. M. Lancet, 1922, Jan., p. 38.
3. Idem. Lancet, 1923, 204: 575–576.
4. Idem. J. Am. M. Ass., 1922, 78: 1885–1887.
5. Idem. J. Pharmacol. & Exper. Therap., 1920, 15: 29–74.

[1] In this connection I refer to the communication of W. F. MacFee and R. R. Baldridge, Ann. Surg., 1930, 91: 329–341, who saw good results in conditions of shock (also as a consequence of great loss of blood) of the infusion into the circulation of for instance 3 to 5 liters of sodium chloride solution.

6. Beck, A. Deutsche med. Wchnschr., 1928, No. 14, 564.
7. Idem. Deutsche med. Wchnschr., 1928, No. 30, 1247.
8. Bosc, F. J., and Vedel, V. Rev. de méd., 1897, 17: 888–905.
9. Idem. Rev. de méd., 1898, 18: 229–279.
10. Ibid. pp. 461–496.
11. Bressot, E. Progrès méd., 1931, March, 481–482.
12. Editorial. J. Am. M. Ass., 1922, 78: 730.
13. Giraud, J., and Silhol, P. Presse méd., 1930, Aug., 1082.
14. Goltz, F. Arch. f. path. Anat., 1864, 29: 394–433.
15. Hamburger, H. J. Researches made in the Physiological Laboratory of the Utrecht University, 1887, 3d Series, No. 10, pp. 35–64 (Holl.)
16. Hoitink, A. W. J. H. Are there "artificial sera" with a peculiar favourable action in hemorrhages? A comparative research on the action of several blood-substitutes in dangerous hemorrhages. Thesis de doct., Utrecht, 1934, February. (Holl.)
17. Idem. Geneesk. Bl., 1934, 32d Series, No. 5. (Holl.)
18. Idem. Nederl. Tijdschr. v. Geneesk., 1934, No. 35, 3937–3952. (Holl.)
19. Holovtschiner, E. Arch. f. Anat. u. Physiol., Physiol. Abteil., Supplement-band, 1886, 232–248.
20. Mac Fee, W. F., and Baldridge, R. R. Ann. Surg., 1930, 91: 329–341.
21. Normet, L. Presse méd., 1925, No. 3, 37.
22. Idem. Paris méd. 1926, July 31.
23. Idem. L'action biologique des citrates métalliques. Brochure Pharmacie. T. Leclerc, Paris.
24. Idem. Bull. et mém. Soc. nat. de chir., 1929, 55: 848–853.
25. Idem. Compt. rend. de l'Acad. d. Sc., 1929, 188: 354.
26. Idem. Bull. Acad. de méd., 1923, 90: 624.
27. Idem. Bull. Acad. de méd., 1924, 92: 1306.
28. Idem. Bull. Acad. de méd., 1924, Dec. 23, 1470.
29. Idem. Bull. Acad. de méd., 1920, Feb. 17 and 24.
30. Siebeck, R. in: Bethe, Handbuch d. norm. u. pathol. Physiol., 1926, 17: 161–222.
31. Simenauer, E. Med. Klin., 1930, 385–388.
32. Weichardt, W., and Unger, H. Deutsche med Wchnschr., 1928, No. 30, 1247.
33 Wong, San Yin. J. Biol. Chem., 1923, 55: 421.

THE HYPERTONIC WET DRESSING

An Experimental Study[1]

FREDERIC W. TAYLOR, M.D., Indianapolis, Indiana

THE exceptional therapeutic value of the wet dressing, and more particularly the hypertonic wet dressing in the care of infected wounds, is an accepted fact. The constant beneficial results seen clinically have established this principle as among the most valuable in modern medicine. Because of this general acceptance, the controversy as to the exact mode of action of the hypertonic wet dressing has long been forgotten.

It was Sir Almroth Wright's contention that a hypertonic solution in contact with a wound acted as a lymphagogue. In this way it drew out lymph which had spent its bacteriocidal energy and called forth fresh lymph together with phagocytic white cells. The outpouring of lymph was considered the all important factor because of the fact that the hypertonic solution disintegrated the white cells and inhibited much beneficial enzymic action.

Taylor, citing numerous experiments on the diffusion of salts and colloids, held that only water was drawn from the wound since the larger protein molecules diffused very slowly through the semipermeable membrane of the capillary wall. Taylor also felt that hypertonic solutions checked the migration of leucocytes to the surface and that those reaching the surface were quickly destroyed.

Present day knowledge holds to this latter belief. That is, only water diffuses out into the hypertonic dressing and salt passes back into the cells of the tissues. This process gradually slows down as an osmotic balance is established. There is a slight but constant diffusion of protein outward. This takes place at a constant rate regardless of the tonicity of the solution used. The hypertonic solution has little or no effect in sterilizing the wound (Landau). It is not known how important a factor the solution is in bringing phagocytic white cells to the infected tissues. Nor is it known how much of a detrimental effect the solution may have on the action of the white cells once they reach the site of infection.

A great deal has been written on the value of hypertonic wet dressings. This has been largely from a clinical and theoretical standpoint. Very little experimental work on this subject has been undertaken.

The data here recorded are the result of the writer's curiosity to know just how much fluid might be withdrawn from a given wound with a given hypertonic solution. It seemed desirable to ascertain whether the amount withdrawn was sufficient in any way to account for the beneficial results obtained clinically. It also seemed important to learn what effect different hypertonic solutions had upon the rate of diffusion of fluid from the wound. The writer has been unable to find any previous work on this particular phase in the treatment of infections. Because of this it was thought that the following report would be of interest.

After starting the work, numerous ramifications of the original problem were suggested. Some of these were studied and comments upon them are also given.

In all, 152 experiments were run on wounds of varying size and age. For the sake of brevity, an individual tabulation of these determinations is omitted. They have been summarized in the discussion of the results and many are indicated in Figures 1, 2, and 3.

The animals used were rabbits. These were chosen because of the ease with which they could be handled during a series of experiments. The blood of a rabbit is slightly more hypertonic than that of man (11) but this slight difference should make little variation in the results obtained. There can be no valid reason for not comparing the findings in these experiments directly with similar situations and conditions in man.

The solutions tested included sodium chloride .85, 2.5, 5, 10, and 20 per cent; magnesium sulphate 16, 32, and 64 per cent; glucose 20 and 50 per cent. A mixture of half glycerine and half alcohol was also used.

[1]From the Department of Pathology, Indiana University School of Medicine, Indianapolis, aided by a grant from the Research Division.

METHODS

The methods used were of necessity somewhat crude since the problem involved open wounds. The action of hypertonic solutions upon these wounds varied to a considerable degree. This was particularly true in the older wounds. In these there were marked differences in response to hypertonic solutions. Also in the older wounds varying amounts of fibrin were deposited upon the wound floor thus impeding a free fluid interchange. For these reasons the use of a granulating wound was largely discarded. Most of the experiments were done on fresh wounds having the abdominal muscle layer of the rabbit for a base. Only a very thin sheet of muscular fascia was allowed to remain covering the muscle. This allowed ample opportunity for a free osmosis between the capillaries of the muscle bed and the solution to be tested.

DETERMINATION OF AMOUNT OF FLUID WITHDRAWN FROM THE WOUND

Using an etherized rabbit with shaved abdomen, a portion of skin and subcutaneous fat was removed. Much of the deep fascia was also excised, only the muscle fascia itself being left to cover the abdominal muscles. Little trouble was encountered from bleeding vessels but when this did occur the vessels were carefully ligated. Dimensions of the wound were taken and its area calculated. The wound areas varied in the different animals from 0.5 to 2.7 square inches. So as to have a standard of comparison, the results obtained from the different trials were corrected so as to show the fluid change for one square inch of bare wound surface.

After the preparation of the wound a portion of a rubber glove was fastened to the surrounding skin margins by means of rubber cement. This proved quite satisfactory and this combination often would remain water tight for 3 to 5 days. Into the portion of rubber glove was then put exactly 5 cubic centimeters of the hypertonic solution to be tested. A gauze fluff was laid over the abdomen and held in place by means of a small jacket. This kept the fluid in contact with the wound and the movement of the rabbit promoted a certain amount of fluid circulation.

After varying time periods (1 to 24 hours) the fluid was drained from the glove and carefully measured. Again 5 cubic centimeters of the same or another hypertonic solution was introduced and the processes repeated. Often the first run was discarded because of fluid loss from moistening the entire area or because of oozing of blood. In so far as possible the experiments were run in succession so that a more accurate comparison might be made of various solutions on the same wound.

The fluid removed from the rubber glove was analyzed to determine the amount of salt present and from that the percentage of salt of this fluid was readily calculated. The methods used in determining the amount of the solute were as follows (5): sodium chloride by Volhard-Arnold's method for chlorides; magnesium sulphate by Folin's method for sulphates, and glucose determination by Benedict's quantitative method. In the tests for sodium chloride and magnesium sulphate, protein was first removed from the samples by precipitation with tungstic acid, and determinations were then made on the protein-free filtrate. A protein estimation by Purdy's quantitative method for albumin was also done on many of the samples.

DETERMINATION OF HYPERTONICITY OF WET GAUZE DRESSING

In this series of experiments it was desired to find out what hypertonicity was present in the gauze next to the wound tissues as compared to the gauze on the outer portions of a wet dressing. Layers of gauze (40–44 mesh) were applied to the same type of abdominal wound previously described. The dressing was saturated with the hypertonic solution to be tested. After varying periods of time (1 to 20 hours) the dressing was removed and the different layers tested for their salt concentration. This was determined by dissolving the salt from the layers of gauze into a known quantity of water and then analyzing this for its salt content.

RESULTS

Amount of fluid removed from wound by hypertonic solution. As previously stated, the tests were corrected so as to give the amount

of fluid given up by a wound 1 inch square in contact with 5 cubic centimeters of hypertonic solution. The solution was held in contact with the wound by means of rubber tissue.

It was found that all the hypertonic solutions used caused approximately the same amount of fluid diffusion from the wound. The amount of this diffusing fluid was 1.2 to 1.5 cubic centimeters per hour for the square inch of wound surface. This constancy was remarkable when the wide range of hypertonic solutions used was considered. These varied from 2.5 per cent sodium chloride with a hypertonicity of 3 (as compared with physiological saline) to 20 per cent sodium chloride with a hypertonicity of over 23. There was no noteworthy difference when magnesium sulphate or glucose solutions were substituted for the salt.

Fluid continued to pour out into the enclosed rubber container until it reached a hypertonicity of approximately 1½ (1.3 per cent for sodium chloride). At this point the fluid started to reabsorb and continued at a rather rapid rate. In Figure 1 these features are shown quite well diagrammatically for 5 and 10 per cent salt solutions. The curves resulting from other hypertonic solutions have been omitted from this graph for clarity. Their upward slope, however, is identical with those illustrated.

There seems to be but one explanation for the fact that approximately the same amount of water is withdrawn from the wound, regardless of the hypertonicity or the agent. In removing such relatively large amounts of fluid the capillaries must of necessity be the source of supply, osmosis taking place through their walls. Solutions having a hypertonicity of 3 can withdraw from the capillary bed of the wound practically the same amount of water as those of much greater hypertonicity. Therefore, within the range of solutions tested, the water diffusing outward must depend upon the volume of blood brought to the wound. Also, this volume was not appreciably increased by the various hypertonic solutions used. From this the conclusion can be drawn that in any wound the amount of fluid removed by a hypertonic solution is directly

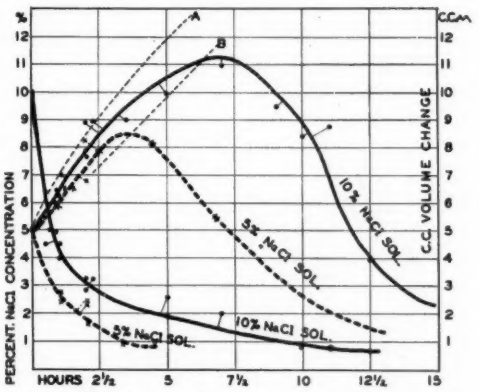


Fig. 1. Showing the changes in volume and concentration of 5 cubic centimeters of 5 and 10 per cent sodium chloride held in contact with a square inch of wound surface. Curves of other solutions have been omitted. However, all tested concentrations of magnesium sulphate, sodium chloride, and glucose showed the same general rate of volume increase and their increase curves fell between the two dotted lines *A* and *B*.

proportional to the vascularity of that wound and bears little or no relation to the type or strength of solution used. This, of course, neglects the initial small amount of water which diffuses from the edematous tissues.

Solute diffusion into wound tissues. It was surprising to learn how rapidly a solution held in contact with a wound lost its hypertonicity. Part of this was of course due to a dilution by the outpouring water. However, a large factor was the diffusion of the salt into the wound. Thus 5 cubic centimeters of a 10 per cent sodium chloride solution in contact with a square inch of wound surface becomes 6.5 cubic centimeters of a 4.2 per cent solution at the end of an hour. In other words, 43 per cent of the original salt diffused into the wound tissues during this first hour. With weaker solutions this loss to the tissues was somewhat less. The same rapid loss of solute by diffusion was found with 20 per cent glucose solution.

It is well known that magnesium sulphate solutions diffuse but slowly into the tissue cells. Because of this they have for some time been advised for use in hypertonic wet dressings. It might then be expected that in our experiments the diffusion loss of magnesium sulphate solution was less than with sodium

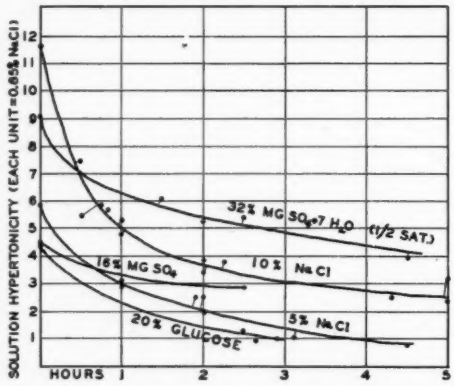


Fig. 2. Illustrating the rapidity of loss in concentration of various hypertonic solutions. It will be noted that the magnesium sulphate solutions maintained their concentrations much better than the other solutions indicated.

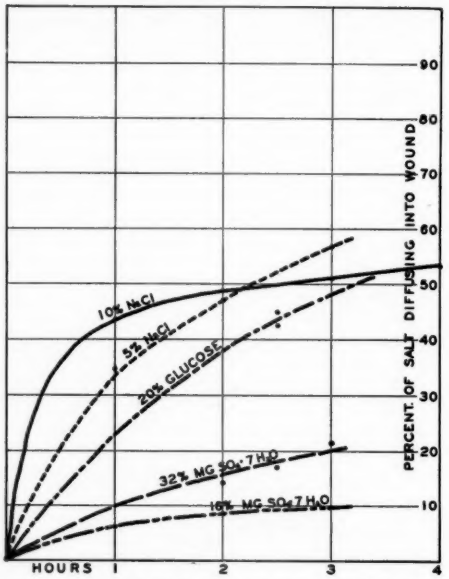


Fig. 3. Per cent of the various salts diffusing into the wound tissues. The relative smaller loss by diffusion of magnesium sulphate is indicated.

chloride or glucose. This was true but nevertheless the loss by diffusion of magnesium sulphate was quite appreciable. When 5 cubic centimeters of a 32 per cent solution (half saturated) was in contact with an inch square wound for 1 hour it became 6.2 cubic centimeters of a 22 per cent solution. This represents a loss by diffusion into the wound of 14 per cent in 1 hour.

The losses in hypertonicity of the various solutions in contact with the wound are shown graphically in Figures 1 and 2. The loss by diffusion is shown in Figure 3. Here it is clearly seen that the loss by diffusion is far less for magnesium sulphate solutions than for others which were tested.

Effects of extremely hypertonic solutions. Several extremely hypertonic solutions were tested upon the wounds. These included 20 per cent sodium chloride, 64 per cent magnesium sulphate (saturated solution at room temperature), 50 per cent dextrose, and half alcohol and half glycerine. All these solutions caused a maximum amount of water to flow from the wound. This, however, only averaged approximately 10 per cent more than the milder hypertonic solutions and was always blood tinged, showing that there had been actual damage to the capillaries. The wound tissues exposed to these very hypertonic solutions were found to be uniformly very edematous. The looser connective tissue assumed quite a gelatinous quality. Much hemorrhage was found beneath the fascial membranes. This gave the wound a dirty brown necrotic appearance. Microscopic sections of the wound tissues demonstrated these same destructive changes.

In the light of this finding, it certainly seems inadvisable to use the extreme hypertonic solution advocated by some (1, 8). This is especially so since they draw but little additional fluid from the wound.

Diffusible protein. The amount of protein diffusing out into the hypertonic solution was quite constant, as estimated by the Purdy quantitative test for albumin. It was proportional to the elapsed time and seemed to have little to do with the hypertonicity or type of solution used. Exceptions to this were in the older wounds and, when extremely hypertonic solutions were used, gross blood appeared in the fluid to be tested. In both instances the amount of protein was quite variable and usually high.

White blood cells. It would, of course, be desirable to determine the number of phago-

cytes drawn forth by the various hypertonic solutions. Attempts were made to do this but were abandoned because of the inaccuracies of such a procedure. The white cells in the very hypertonic solutions were largely destroyed and their remnants clumped together in plaque like masses. Those observed in solutions of lower hypertonicity were destroyed to a lesser degree, but counting chamber methods still gave results too variable to report.

Gauze dressing analysis. An analysis of the layers of a gauze dressing to determine the hypertonicity of these different layers was interesting. This was done with solutions of 5 and 10 per cent sodium chloride, 32 and 64 per cent magnesium sulphate. It was found that the innermost layers of gauze (those next the wound) were markedly decreased in their hypertonicity as compared with the outer layers. Thus when both 5 and 10 per cent sodium chloride solutions were used to saturate the dressing, the first two thicknesses of gauze next the wound had a 1.1 to 2 per cent concentration after 1 hour. This would indicate that it is only this hypertonicity (1.1 to 2 per cent sodium chloride) which is effective in drawing water from the wound.

When magnesium sulphate in the solutions previously indicated were used, slightly higher values were obtained. With the saturated solution (64 per cent), the innermost two layers were found to contain a 14 per cent solution. With the half saturated solution these same layers contained an 8 per cent solution. It should be stated that an isotonic solution of magnesium sulphate is 3.52 per cent ($MgSO_4 . 7 H_2O$).

Another finding of clinical interest was the fact that when there was the least bit of bloody ooze from the wound, the two inner gauze layers were quite isotonic. Therefore the hypertonic solution would be absolutely ineffective in extracting fluid by osmosis. As there is always a bloody ooze from a recently incised abscess, it should be remembered that action of a hypertonic wet dressing to such a lesion is nil as regards its water extracting power.

EVALUATION

It has been shown that the amount of fluid capable of being withdrawn by a hypertonic solution from 1 square inch of wound surface is 1.2 to 1.5 cubic centimeters per hour. This amount varies between these figures regardless of the hypertonicity or nature of the solution. In general the more concentrated solutions gave the higher figure but to all practical purposes they were identical. This at least held true for solutions with a hypertonicity between 3 and 23 (2.5 and 20 per cent sodium chloride).

The values given are maximal for the animals used. They represent figures for new wounds with vascular muscle bases. In older wounds which had started to granulate and the surfaces of which were partly covered by fibrin, the values varied to a considerable extent in different animals and were found to be lower.

It is pointed out that the fluid withdrawn by a hypertonic solution is water and not serum similar to that seen in burns (7,9). It contains only the amount of protein material which would normally diffuse from the wound. There is no increment of this caused by the hypertonic solutions. The value of this withdrawal of water from the wound seems to the writer to be a debatable question. For, after the initial dehydration of the surface tissues, the continued outpouring comes from the blood vessels themselves and is directly dependent on the vascularity of the area. Also in all wounds except those exposed to the lower concentrations of magnesium sulphate, the wound tissues continued to absorb enough salt to maintain in themselves quite an edematous state.

It has been stated that an increased flow of water to the surface brings an increased number of phagocytes (4). This seems probable but the amount of this increase is still unknown. Also the literature relating to the specific ion action (2) and enzymic action resulting from the use of various solutions is unconvincing.

It should be further pointed out in the light of the foregoing experiments on wet dressings that an effective hypertonic solution reaches only the superficial tissue. That the deeper tissues containing the active infection can not possibly be reached by the salt solution is quite evident.

Wherein, then, lies the great value of the hypertonic wet dressing? It is thought that by far the chief benefit derived from this type of dressing is its poulticing action. This keeps the skin soft and pliable. It prevents crusting of the wound and allows drainage to continue. Above all it soon becomes warmed by the body and this markedly increases the flow of capillary blood (3), thus improving the defense mechanism against infection.

Bearing out this contention is the fact that isotonic saline and even hypotonic solutions (1: 5,000 mercuric chloride) have been seen to give the same beneficial effects noted in hypertonic solutions.

It is not the purpose of this paper to discredit the use of hypertonic solutions but merely to point out that the withdrawal of fluid which they effect from the infected wound is of only minor importance. Their principal benefit must be from a poulticing action. It would seem that the most beneficial results might be expected from a mildly hypertonic magnesium sulphate solution (16 per cent $MgSO_4 \cdot 7\,H_2O$).

REFERENCES

1. Besley, F. A. Problems involved in treating compound fractures. Surg., Gynec. & Obst., 1934, 59: 354.
2. Gaza, W. Von. Effect of hypertonic salt solution on granulation tissue. Zentralbl. f. Chir., 1923, 50: 858.
3. Goldschmidt, S., and Light, A. B. The effect of local temperature upon the peripheral circulation. Am. J. Physiol., 1927, 73: 146.
4. Griess, W. R. Some effects of solutions on open wounds and their practical application. Cincinnati J. Med., 1922, 3: 200.
5. Hawk, P. B., and Bergeim, O. Practical Physiological Chemistry. 9th ed. Philadelphia: Blakiston's Son Co., 1926.
6. Landau, H. Experimental research on hypertonic saline in the treatment of wounds. Arch. f. klin. Chir., 1921, 115: 621.
7. Landis, E. M. Capillary pressure and capillary permeability. Physiol. Rev., 1934, 14: 404.
8. Roberts, J. E. H., and Statham, R. S. S. The salt pack treatment of infected gunshot wounds. Brit. M. J., 1916, 2: 282.
9. Taylor, K. Mechanism of saline dressings. Brit. M. J., 1916, 2: 321.
10. Underhill, F. P., Kapsinow, R., and Fisk, M. E. Studies on the mechanism of water exchange in the animal organism. Am. J. Physiol., 1930, 95: 315.
11. Wagoner, G., and Custer, R. P. A Handbook of Experimental Pathology. Springfield: Charles C. Thomas, 1932.
12. Wright, A. E. Memorandum on the treatment of infected wounds by physiological methods. Brit. M. J., 1916, 1: 793.

CLINICAL SURGERY

FROM THE NEW YORK HOSPITAL AND CORNELL MEDICAL COLLEGE

COLOSTOMY OF THE TRANSVERSE COLON

FRANK GLENN, M.D., NEW YORK, NEW YORK

IN A recent publication entitled "Origins and Evolution of Colostomy," Dinnick, of London, reviews the history of colostomy. He refers to the biblical book of Judges, in which we find an account of the foul murder of Eglon, King of Moab, by Ehud. Ehud stabbed him in the belly with his dagger and "the dirt came out." This may be the earliest written report of opening the colon, but hardly can it be considered a record of a therapeutic colostomy. The first deliberate colostomy is ascribed to Littré, who, in 1710, devised this operation for the treatment of imperforate anus. That he actually performed such a surgical procedure we have no evidence. However, Pillore, DuBois, Duret, and Desault, in the eighteenth century, opened the sigmoid colon in treating imperforate anus. Fine is said to have performed the first colostomy of the transverse colon quite by accident in an attempt to open the small intestine through a midline incision just above the umbilicus. The nineteenth century witnessed an increase in colostomies which then were used also in the treatment of intestinal obstruction due to malignancy. In 1853, Hawkins reports that 44 such operations had been recorded in the literature and that the procedure was attended by a 50 per cent mortality due to the fact that it was invariably followed by peritonitis. The work of Pasteur and Lister, which so revolutionized surgery, increased the safety of this procedure.

Inguinal colostomy originally was the operation of choice, but later was supplanted by lumbar colostomy. The pioneers in this field of surgery encountered difficulty in closing the artificial anus which they had made. Prior to the nineteenth century it was believed that the section of bowel which had been used for the colostomy must be resected. Obviously this entailed an intestinal anastomosis, a procedure of such magnitude in those days that it carried with it a high mortality. This difficulty was obviated when it was found that a small opening in the bowel sufficed, for this was simple to close. The repaired bowel, then, could be returned to the abdomen through the defect in its wall with or without entering the peritoneal cavity.

A review of the last 25 years shows that surgeons have directed their efforts mainly toward perfecting the permanent colostomy. With this aim in view, they have devised several ingenious methods of procuring control of the artificial anus. The horror of patients, ignorant of colostomy, when they are told that such a procedure is imperative in the treatment of their disease, is minimized if they can be promised some means of control. It has been the prevailing opinion that the best results are obtained by placing the colostomy near the site of the obstruction, a logical procedure when permanent colostomy is concerned. It is the object of this discussion to point

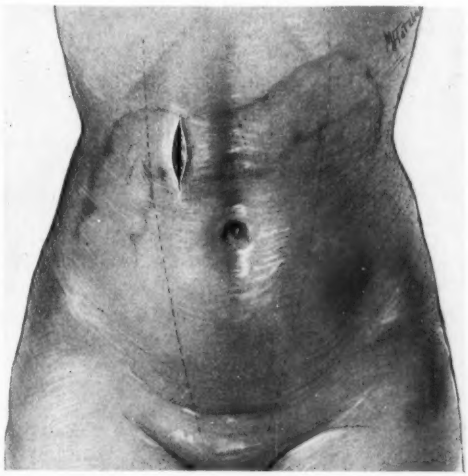


Fig. 1. The transverse colon is approached through a vertical incision, 6 centimeters or more in length, over the midportion of the right rectus muscle just above the umbilicus.

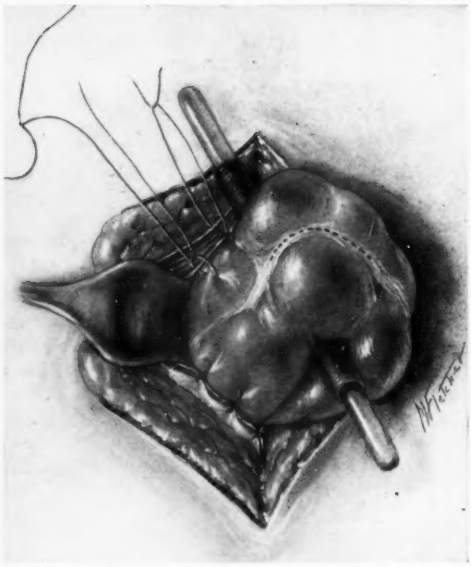


Fig. 2. With interrupted sutures of median silk the peritoneum is secured to the bowel where it emerges from the abdominal cavity; when these sutures are tied the same silk is used to bring the anterior sheath together. The dotted line indicates the incision for the colostomy tube.

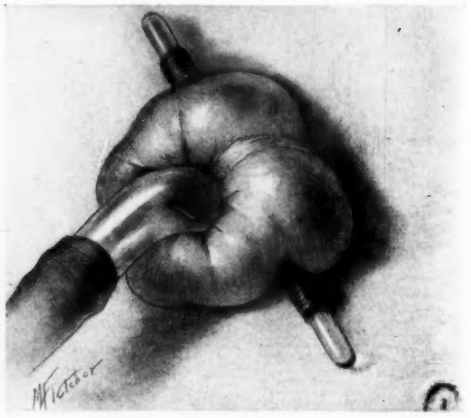


Fig. 3. The large caliber glass tube is anchored with a pursestring suture. The glass rod is shown in place under the exteriorized loop of intestine.

out the advantages of establishing a temporary colostomy at some distance from the lesion.

The description of transverse colostomy is given, without claim to originality, with the idea of promoting this operation as an important step in the treatment of lesions of the descending colon, the sigmoid, and the rectum, a step which simplifies the eradication of the lesions. The rationale of this operation, the technique of the surgical procedure, the care of the completed colostomy, and its closure will be discussed in turn.

A temporary colostomy is designed to decompress the large bowel partially or wholly obstructed by a lesion below the splenic flexure, in preparation for the removal of the lesion. When an obstruction has persisted for some time, the wall of the bowel proximal to the obstruction becomes edematous and sometimes hypertrophic. The anastomosis of a collapsed segment of bowel below the obstruction, to an edematous hypertrophic portion above it, is a procedure which is rarely satisfactory. If the bowel above the lesion is decompressed and kept evacuated, it is given an opportunity to return to a normal state before the removal of the lesion is attempted; the anastomosis, then, can be carried out under more favorable conditions. A preliminary colostomy is equally important as a means of improving the patient's general condition, in preparation for the formidable procedure of resection which is to follow. A malignant tumor of the large bowel is rarely a rapidly growing lesion and the time consumed in building up the patient's resistance is well spent.

There are two arguments in favor of transverse colostomy. First, there is no portion of the large bowel, with exception of the rectosigmoid, which is as freely movable as are the hepatic flexure and the first part of the transverse colon; long mesenteric attachments facilitate the delivery into a right rectus wound of this section of bowel. The intestine, through which the fecal stream passes before reaching this region, frees the contents of most of the digestive elements which make the care of an ileostomy or cecostomy so difficult. Second, a transverse colostomy, high on the right side of the abdomen, is far removed from the operative field in the resection of the lesion, and does not endanger the asepsis of this major operation.

Transverse colostomy is not a major procedure; it can be carried out under local anesthesia with little danger to the patient immediately, though he may be in poor condition because of long standing obstruction or of complications of intestinal pathology necessitating surgical intervention. Even though an exploration following the colostomy reveals an inoperable growth, warranting a permanent artificial anus, nothing has been lost

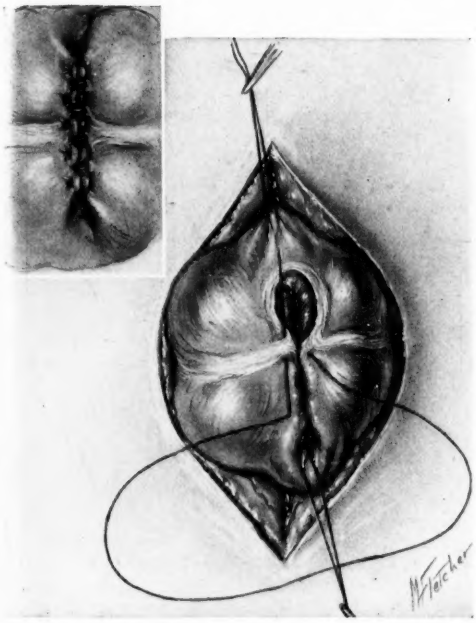


Fig. 4. The incision into the colon is closed transversely with respect to the axis of the bowel. Silk traction sutures are placed in the intestinal wall laterally; with traction exerted upon these sutures, a continuous catgut suture is introduced through the entire wall to unite the serosa on either side and thus to invert the mucosa.

by the preliminary emergency colostomy of the transverse colon which is closed without difficulty. If the tumor can be resected, this type of colostomy offers the greatest protection against contamination of the clean wound. In an analysis of the deaths in any series of cases treated for malignant disease of the colon below the splenic flexure, it will be seen that infection is the most serious complication.

THE OPERATION

The transverse colon is approached through a vertical incision, 6 centimeters or more in length, over the midportion of the right rectus muscle just above the umbilicus (Fig. 1). After the skin and subcutaneous tissues have been incised, the anterior rectus fascia is divided; the muscle fibers on either side of the incision are freed and the muscle split with a blunt instrument to the full extent of the skin incision. The posterior rectus sheath, which is now exposed, is grasped with a forceps and incised with the peritoneum lying below it. A hemostat is placed on each side of the

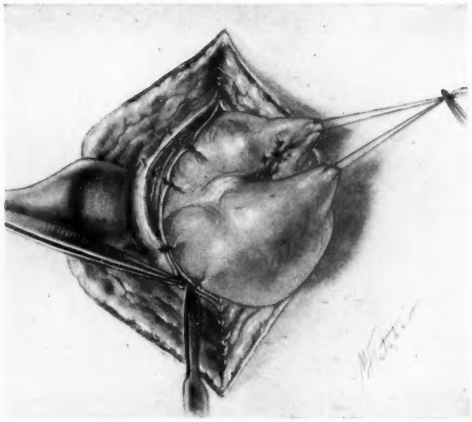


Fig. 5. After closure of the bowel, the fascia is separated from the point of union with the peritoneum by dividing the silk sutures as placed in Figure 3.

opening in the peritoneum, which is extended the whole length of the incision. The colon usually lies directly in the field and is now delivered through the abdominal wound and inspected. If the omentum covering the bowel is freed at its attachment to the extramesenteric border, it may be returned to the abdominal cavity. A rent is made in the transverse mesocolon under the loop and a glass rod is inserted through the opening to aid in maintaining the bowel on the outside of the abdomen.

The closure of the wound is designed (1) to anchor the intestine, (2) to prevent the peritoneum from tearing, (3) to isolate the rectus muscle, and (4) to avoid herniation of the bowel. With interrupted sutures of medium silk the peritoneum is secured to the bowel where it emerges from the abdominal cavity (Fig. 2). Sutures are placed above and below the glass rod and at either end of the peritoneal incision to prevent it from tearing. When this level of the wound has been closed and the sutures tied, the same silk is used to bring the anterior sheath together. In this way the muscle is isolated on either side of the wound where it cannot attach itself to the intestine; this facilitates the eventual closure of the colostomy. Skin sutures are introduced at the extremities of the wound so that the skin is approximated snugly to the bowel without tension. If the abdominal wall is thick, an attempt is made to sew the fascia to the skin, to prevent the bowel from pocketing under it in the subcutaneous fat. If this procedure is not carried out in stout patients, the bowel may retract below the

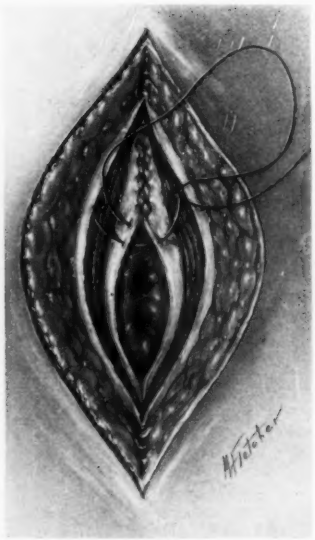


Fig. 6.

Fig. 6. The closure of the peritoneal layer is accomplished by the application of a continuous chromic catgut suture.

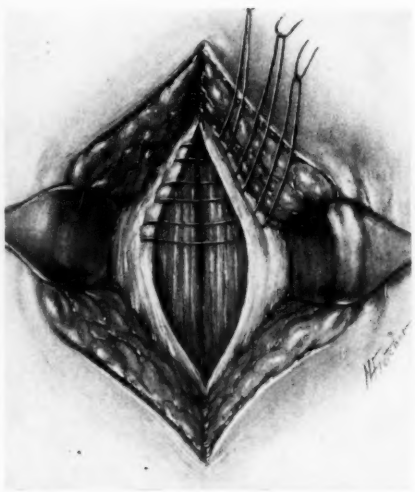


Fig. 7.

Fig. 7. The external rectus sheath is overlapped and sutured with interrupted chromic sutures.

Fig. 8.

Fig. 8. The external rectus sheath closed.

surface and close spontaneously. The obese patient with a thick abdominal wall is best guarded against abscess formation by allowing 36 to 48 hours to elapse before opening the colostomy.

At the completion of the operation, vaseline gauze is applied to the skin where it joins the bowel wall and the bowel is overlaid with the same material. The final dressing is a soft gauze pad held in place loosely so as not to interfere with the passage of gas and fluid fecal material through the exteriorized loop. This dressing is not disturbed until the bowel is opened.

Decompressing the bowel at the time of operation. In patients who have been distended for a long time or in whom the distention is causing marked discomfort, it may be necessary to decompress the bowel at the time of operation. With all steps of the procedure completed, including the application of the vaseline gauze over the loop of colon, a small area is exposed and two pursestring sutures are placed so as to encircle the point selected for the introduction of the needle. With a bichloride sponge protecting the bowel, a lumbar puncture needle (No. 20) is inserted into its lumen, through which the gas escapes. When the tension has been relieved, the pursestring sutures are drawn tight and secured around the needle as it is withdrawn. The site of the puncture is cleansed with alcohol and a bichloride sponge is held in place over it by the vaseline gauze. If the bowel is distended with fluid feces as well as gas, it may be considered wise immediately to institute continuous drainage; for this purpose either a catheter or a glass tube may be inserted into the loop and secured with sutures. Care must be exercised not to contaminate the fresh wound with fecal material. Pursestring sutures are placed as described for the needle puncture. The bowel, protected with bichloride sponges, is held with forceps and incised with a scalpel; the catheter is introduced through the opening. The pursestring sutures are secured about the catheter and the bowel wall drawn about it by a series of medium silk mattress sutures after the method of Witzel for a distance of 3 centimeters from the bowel wall opening. A small rubber tube attached to the end of the catheter leads fecal material into a bottle by the bedside. If a glass tube is used instead of the catheter, it is introduced and anchored in the same way. The tube should be L-shaped and small, for it is difficult to avoid contamination of the wound if too large a tube is introduced at this time. The immediate establishment of drainage is never the method of choice, but serves when relief from distention is imperative.

Opening of the colostomy. It is much safer to delay the opening of the colostomy until the second or fourth postoperative day, for the danger of contamination and infection of the wound is diminished by waiting. If the patient is not suffering acute symptoms of obstruction and the colostomy is a step in preparation for the major operation, this problem need not be faced, for the fecal stream follows its natural course. When the lesion in the lower bowel is causing grave signs of obstruction and the restriction of food and fluids by mouth fails to relieve the discomfort of the patient, the bowel must be opened earlier.

The incision into the bowel, made with a scalpel or cautery, is longitudinal and carried through the tenia opposite the mesenteric attachment. It should be only of sufficient length to admit the tube, which in this case is of larger caliber than the one described for immediate decompression of the bowel. This larger tube (2 centimeters in diameter) does not so easily become clogged by semifluid feces, and a catheter may be introduced into the bowel through it to wash out solid fecal material. The tube is anchored as described above (Fig. 3).

The care of the colostomy before the tube is removed. The tube which is inserted into the bowel when the colostomy is opened usually stays in place until the sixth or seventh postoperative day. Before it is removed, the care of the colostomy is not difficult, for the fecal material drains through it directly into a bottle by the bedside. The consistency of the fecal stream can be controlled by diet and by the administration of mineral oil or other mild laxatives. If the intestinal contents are not liquid, the tube may become clogged, but irrigation will relieve any obstruction of this kind.

Removal of the glass rod. The glass rod, introduced through the mesentery under the loop of bowel delivered into the wound, is usually removed before the drainage tube is withdrawn. It may be left in place (a) if the intestinal loop tends to retract, as it may if a short mesentery keeps it under tension, or (b) to prevent any fecal material from passing into the bowel below the colostomy.

The care of the colostomy after removal of the tube. After the drainage tube has been removed, there is no way of carrying the fecal stream beyond the confines of the dressing. Although this is not as serious a matter in transverse colostomy as it is in ileostomy or cecostomy, the skin may become irritated by contact with feces. This excoriation may be prevented by the application of aluminum paste (aluminum metal 50 parts, zinc oxide 450 parts), which adheres closely to the skin. The coat of paste must be renewed every 2 or 3 days. An absorbent dressing is kept over the colostomy until it is completely healed.

The care of the bowel distal to the colostomy. When the lumen of the bowel has been completely occluded by a lesion, the segment of intestine between the obstruction and the colostomy requires particular care. Daily irrigations with saline will cleanse it of fecal material and débris; instillations of a saturated solution of magnesium sulphate will reduce the edema. Provided these treatments are given with care not to cause hemorrhage, they are the best means of restoring the bowel to its normal state. If the obstruction at the site of the lesion has not been complete, through and through irrigations with saline followed by instillations of oil will keep the gut clean and will tend to allay some of the congestion. This procedure should be carried out once a day.

The care of the colostomy by the patient. As soon as the patient is ambulatory, he must be taught the means of avoiding unnecessary discomfort and inconvenience from his colostomy. He learns to regulate his diet so that his stools are not too soft or liquid. He becomes familiar with the sensations which warn him of impending movements; this enables him to adjust his life so that the colostomy causes him the minimum of inconvenience. A colostomy bag may add to his feeling of security at first, but it is frequently discarded as soon as the patient discovers that a degree of constipation enables him to reduce the evacuations of his bowels to one or two a day. A dressing of absorbent material guards against soiling.

Closure of the colostomy. Closure of the colostomy may be accomplished in one of two ways, i.e., extraperitoneally or intraperitoneally. The exteriorized bowel segment must be liberated before its closure can be undertaken. The initial steps are the same in both procedures. An incision is made in the skin following the outline of the old scar, but leaving a narrow margin of skin attached to the bowel. The subcutaneous tissues are bluntly dissected off of the bowel down to its junction with the external rectus sheath. The sheath is divided, again leaving a margin around the entire loop of colon. The muscle which is now exposed, is reflected away from the junction of the external sheath and the peritoneum; the line of silk sutures which united these surfaces at operation will act as a guide to this junction and having served this purpose they may be removed (Fig. 5). The margins of skin and external rectus sheath which were left attached to it may now be stripped off of the bowel by sharp dissection. Excepting for its attachment to the internal sheath

and peritoneum, at the base of the wound, the intestine now lies free and the closure of the opening in the bowel may be carried out as follows: The incision into the colon, which, as will be recalled, was made in a longitudinal direction, is closed transversely with respect to the long axis of the bowel, in order to prevent narrowing of the lumen. Silk traction sutures are placed in the intestinal wall laterally; traction on these sutures will bring the sides of the opening together across the long axis of the bowel. In this position a continuous catgut suture is introduced through the entire wall to unite the serosa on either side and thus to invert the mucosa. A series of interrupted mattress sutures of silk are now placed in the serosa and these in turn are reinforced by single interrupted sutures of the same material placed between the mattress sutures (Fig. 4). At this stage in the procedure the operation is interrupted while the operative field is cleaned, the wound redraped with clean towels and the entire surgical set-up replaced by a new one. The closed bowel is now invaginated through the defect in the abdominal wall, and over it the peritoneum is approximated with a continuous suture of chromic catgut (Fig. 6). The muscle is freed, so that it may resume its normal position across the center of the wound. The external rectus sheath is overlapped and sutured with interrupted stitches of chromic catgut (Figs. 7 and 8). One stay suture holds the skin, subcutaneous tissues, and fascia together; a rubber tissue drain is inserted down to the fascia, and the skin is approximated with interrupted sutures of fine silk.

When the wound has been opened down to the peritoneum as described, and the bowel, thereby, is not sufficiently liberated to permit its closure, or if there be herniation of omentum or any of the abdominal contents between the bowel wall and the peritoneum, as may sometimes be the case, then the peritoneum must be opened. An incision is made close to the intestinal wall and carried around the entire loop. This makes it possible to draw the bowel further out through the wound. With the peritoneal cavity carefully protected with gauze pads, the closure of the orifice in the bowel is undertaken as previously described. If adhesions are present between the colon and the peritoneum, these are freed and the bowel is returned to the abdominal cavity. The peritoneum is closed with a continuous suture of chromic catgut and the subsequent steps in closing are as described.

Intraperitoneal closure is never the method of choice; but although the peritoneal cavity must be considered grossly infected in an intraperitoneal closure, localized abscess formation or peritonitis rarely follows this procedure—a fact which gives evidence of the establishment of a local immunity.

Postoperative care after closure of the colostomy. Nothing is given the patient by mouth for a period of 24 hours after closing the colostomy; and for an additional 48 hours the intake is restricted to clear fluids. This routine has been adopted in an effort to reduce peristalsis to a minimum during the first postoperative days. If the bowel can be kept quiet for 48 to 72 hours, there is little danger of intestinal obstruction or of a fecal fistula developing at the site of the closure. Seventy-two hours after operation the patient is given a soft diet and mineral oil as a laxative.

The drain is removed at the end of 48 hours. If there is an unusual amount of reaction around the wound at this time, warm moist saline dressings are applied.

The patient is allowed up on the eleventh postoperative day.

SUMMARY

1. A brief history of colostomy is given, including reference to the recent developments.

2. Transverse colostomy is recommended as a step in the preparation for the removal of a lesion of the lower bowel or rectum.

3. The rationale of this operation, the technique of the surgical procedure, the care of the completed colostomy, and its closure are discussed.

BIBLIOGRAPHY

1. Desault, P. J. J. de chir. de Desault, 1794, 4: 248.
2. Dinnick, T. Origins and evolutions of colostomy. Brit. J. Surg., 1935, 22: 142.
3. Dubois. Rec. periodique Soc. méd. de Par., 1797, 3: 123.
4. Duret, C. Rec. periodique Soc. méd. de Par., 1798, 4: 45.
5. Fine. Ann. Soc. de Montpellier, 1797, 6: 34.
6. Hawkins, C. Med. Chir. Tr., 1852, 35: 85.
7. Littré. L'Hist. Acad. d. sc., 1710, p. 37.
8. Pillore, H. Gaz. de hôp. de Par. 1840, 2d S., 22.

KRAUROSIS VULVÆ (LEUCOPLACIA) AND SCLERODERMA CIRCUMSCRIPTA

A Comparative Histological Study[1]

LLOYD W. KETRON, M.D., and F. A. ELLIS, M.D., Baltimore, Maryland

IN July, 1932, a patient, with the diagnosis of kraurosis vulvæ, was referred to the Department of Dermatology from the Gynecological Dispensary for advice because of the severe itching associated with the disorder. During the examination, it was discovered that she had lesions also on her body resembling those of a variety of circumscribed scleroderma which has been described as white spot disease. This association stimulated us to make a comparative histological study of these two affections including, also, several cases of the morphea type of scleroderma. The patient referred to will be considered in full, and a brief summary of a second case of white spot disease, without vulvar lesions, will be included. The histological findings in these cases will be compared with those of kraurosis vulvæ, the material for which was obtained mainly from the Gynecological Laboratory through the courtesy of Dr. Cullen.

REVIEW OF LITERATURE

A. *Kraurosis vulvæ.* This name was introduced by Breisky in 1885 to describe a condition of the female genitalia characterized by a peculiar atrophic shrinking of the skin affecting the vestibule, small labia, inner surfaces of the large labia up to the posterior commissure and bordering part of the perineum. The frenulum and prepuce disappear and the small labia are represented only by a white line. The affected skin is white and dry where retraction is most pronounced, while in other areas it is shiny, dry, pale, reddish gray with whitish spots and dilated capillaries. The condition causes a marked vestibular stenosis interfering with childbirth and coitus.

Since kraurosis in the restricted Breisky sense is usually associated with a spotty or diffuse whitish appearance resembling leucoplacia, a great deal of confusion has arisen as to the relationship of these two conditions. Some writers believe that leucoplacia and kraurosis are two distinct diseases, while others consider them different manifestations of the same pathological process. In the former group, Berkeley and Bonney take the most extreme view; their description of the two affections as abstracted by Graves and Smith, is as follows:

Leucoplacic vulvitis is a chronic inflammatory condition of unknown origin characterized in its early stages by marked hyperemia and cellular activity, and in its later phases by marked epithelial hypertrophy, and a thickened, sclerosed, and retracted condition of the subepithelial tissue. The whole of the vulva may be implicated with the exception of the vestibule and orifice of the urethra, which are never affected. It may extend laterally to the folds of the thigh and posteriorly to the external perineum and the skin around the anus. There are four clinical stages:

First stage: reddening, swelling, excoriation, and dryness.

Second stage: retraction with thickening, decrease in size of the greater and lesser lips, and change of color from red to white.

Third stage: cracks and ulcers with discharge and bleeding; tendency to carcinomatous change.

Fourth stage: complete involution; vulval surface smooth, shiny and white; disappearance of labia minora and clitoris from contraction of the subepithelial tissues; cessation of pruritus.

The symptoms are intense pruritus in the second and third stages and pain with acute sensitiveness in the third stage from the exposure of nerve endings in the cracks and ulcers. There are no symptoms in the fourth stage.

Kraurosis vulvæ consists of an atrophic condition of the vulva associated clinically with stenosis of the vaginal orifice and pathologically with certain changes in the dermis. It may involve all the surface of the vulva as far as the skin borders of the labia majora, and the skin of the perineum and anal region. Kraurosis vulvæ is divided into two stages:

First stage: the mucocutaneous surface, red and glistening, is dotted over with small patches varying in color from bright red to purple. The urethral orifice is in a caruncular condition.

Second stage: the mucocutaneous surface becomes yellow like that of a fatty liver. The surface ridges are obliterated. The vaginal orifice is greatly contracted; the labia minora and clitoris disappear; the mons veneris atrophies; the pubic hair breaks off or falls out. The condition is one simply of retraction and thinning. Pruritus is one of the rarest symptoms, the chief complaint being that of dyspareunia. In the first stage, the parts are sensitive, especially to the passage of urine.

Graves and Smith on the other hand, maintain that Berkeley and Bonney's leucoplacia corresponds to what clinicians generally, at least in America, call kraurosis or if they are more exact, kraurosis with leucoplacia, and that their kraurosis is clinically a marked or progressive genital atrophy. Graves and Smith believe that leucoplacia and kraurosis are phases of the same pathological process, and while they recognize the inadequacy of the term "kraurosis," since it characterizes only the shrinking stage of the process, they would let this term be the nickname rather

[1] From the Departments of Dermatology, Pathology and Bacteriology, Johns Hopkins Medical School. Read at the meeting of the American Dermatological Association, Inc., New York City, June 7–9, 1934.

of the whole disease, which, beginning with an irritative vulvitis, is signalized by pruritus, undergoes superficial epidermal changes in the form of leucoplacia, and deeper dermal changes that result in shrinking and retraction.

These opinions will serve to illustrate the confusion existing with reference to these two processes and in the present communication, we will use the terms "leucoplacia" and "kraurosis vulvæ" more or less interchangeably.

The histological findings of different authors in kraurosis and leucoplacia have varied considerably. In one of Breisky's original cases studied by Professor Chiari, an involutionary process was found in the upper corium the substance of which was sclerotic and glassy. In some papillæ, but more specially in the deeper layers of the cutis, there was a small, round cell infiltration. The epidermis showed a hyperkeratosis with shortening of the rete pegs.

Berkeley and Bonney describe the histology of leucoplacia in several stages:

1. Swollen epithelium, increased vascularity, and lymphocytic infiltration in the cutis.

2. Lymphocytes still conspicuous, plasma cells appear, and there is an increased number of large, hyaline, fixed connective tissue cells normal to the part. The sustentacular elements become altered, the white fibers are decollogenized, and become more hyaline in appearance, with a loss in many areas of the elastica producing a zone between the epithelium and deeper tissues. New lymph nodes appear containing areas showing cell division. There is marked hypertrophy of the epithelium.

3. Cellularity of cutis begins to give place to a fibrosis and many of the inflammatory cells disappear. There is a redeposit of collagen around the fibroglia fibers of the fixed connective cells, which in the preceding stage had been greatly increased in number. The previously rarefied tissue now becomes denser than normal, hypertrophy of epidermis persists, but a marked hyperkeratosis has developed. There is total absence of elastica.

Final stage: Complete sclerosis, very few cells remain, atrophy of epithelium.

The histology of kraurosis vulvæ according to these authors is quite unlike that of leucoplacia. In kraurosis, the subepithelial connective tissue exhibits marked patchy cellularity. In the clinically red areas there may be massive plasma cell proliferation, mixed with, or surrounded by lymphocytes and polymorphonuclear leucocytes. A striking feature is the intercalation of the leucocytes between the epithelial cells. The elastic tissue is present except in the masses of plasma cells. The epidermis is thinner than normal.

Jayle and Bender in writing on leucoplacia of the vulva, emphasize particularly the changes in the epidermis and believe that the thickening of the granular layer both in its cellular component as well as the number of granules in the cells is pathognomonic of the affection. They admit, however, that this may fail in certain stages of the process, when a series of alterations irritative or degenerative occur. The eleidin (!) layer may then atrophy and disappear. The dermis proper is markedly altered. The connective tissue is dense and fibrillary, and there is a considerable leucocytic infiltration more marked in the upper zone. The infiltration is composed mostly of small mononuclear cells, abundant plasma cells, and a few polymorphonuclear and mast cells. The collagenous tissue is abundant but does not take the color by Van Gieson's stain as intensely as normal. The elastic tissue is augmented, thickened, and degenerated in the deeper layers. In the upper layers, it is fine and undulating but not increased. They state that it is certain that leucoplacia and kraurosis vulvæ can co-exist, but they had followed cases of the latter affection for years that did not develop leucoplacia. Later on, Jayle looked on kraurosis as the end stage of ordinary vulvar sclerosis. Its histology was characterized by alterations in the epidermis, which was usually atrophied, and a very dense sclerosis in the cutis which was rich in collagen and degenerated elastica.

Szasz, who believes that kraurosis vulvæ is the end stage of leucoplacia found in the latter a high degree of acanthosis and hyperkeratosis, a loose connective tissue relatively poor in elastica and rich in collagen; while in kraurosis there was atrophy of the epidermis associated with a firm connective tissue, almost free of collagen but rich in degenerated elastic tissue.

Gårdlund was struck by the edema and the peculiar elastic tissue changes (hyalinization) which were present in the histological material from 5 of the 6 cases which he reported. In Case 1, some of the papillæ had a homogeneous, glassy, structureless appearance, while others presented an interstitial edema with a stretched reticular connective tissue. In Case 2, the papillæ were edematous with a homogeneous, hyaline or fibrillar appearance, while in Case 3, the entire subepithelial layer was markedly hyalinized. Interstitial edema was present only on the border. He does not believe that there is an increase in connective tissue, but due to the edema the bundles are not only swollen but may be ruptured. A cellular infiltration was present in the lower cutis below the changed elastic tissue. The elastic tis-

sue was absent in the upper edematous or hyalinized areas, while it seemed thicker than normal in the lower unaffected layers of the cutis.

The author believes that the epidermal changes are relatively unimportant, and that the hyperkeratosis and thickening occasionally met with are due entirely to external irritation.

In Peter's case the epidermis was raised up by an exudate containing leucocytes, fibrin, pigment, and amorphous masses. Connective tissue was structureless, and there was a round cell infiltration in the lower cutis with atrophy of elastica.

Goerdes found in the corium a peculiar, glistening, glassy appearance of the connective tissue which had lost its fibrillar appearance. It was poor in vessels and cells, and elastic tissue was absent. There were collections of cells in the subcutaneous tissue. The epidermis was atrophic.

Terruhn believes that there is an intimate relationship between leucoplacia (he calls it leucoderma and the most characteristic change is the loss of pigment) and kraurosis vulvæ but they are not always associated. In well advanced cases of kraurosis vulvæ, leucoplacia can always be found histologically. In the early stage of the disease, there is hyperplasia of the epidermis and, most important, disappearance of the pigment in the basal layer. This is accompanied by a marked edema in the cutis causing a pressure atrophy of the connective and elastic tissues. The former degenerates, appears homogeneous and swollen, but does not completely lose its structure and nuclei. This is followed by a regenerative stage manifested by a loss of the edema and a cellular reaction composed of capillary sprouts, connective tissue and plasma cells, lymphocytes, and a few polymorphonuclears. He interprets this as granulation, and not inflammatory, tissue. In the atrophic stage there is marked atrophy of the epidermis and the granulation tissue in the cutis has been replaced by a firm, fibrous connective tissue. All three stages may be found in the same section.

Graves and Smith, in the histological study of 18 cases, which showed the condition of kraurosis, found that the squamous epithelium was thinner than normal, the papillæ being short and thin or completely flattened out. The corium was very dense, elastic tissue was entirely absent, glands and hair follicles wanting, blood capillaries sparse, and throughout there was a greater or less round cell infiltration. In all of their specimens, however, areas were found which showed leucoplacia, i.e., a thickening and hyperkeratosis of the epidermis. They state that when leucoplacia is present, the corium is denser than normal but less so than in kraurosis alone. Blood capillaries are infrequent, gland and hair follicles are sparse and atrophied, elastic tissue is decreased, and there is always a marked infiltration of round cells. In other words, the only essential difference between leucoplacia and kraurosis, is the greater activity in the former of the squamous epithelial layer.

Taussig prefers the name leucoplacic vulvitis reserving the term kraurosis for those cases in which there is a complete symmetrical atrophy of the labia and prepuce with flattening of the folds. He feels that it is the leucoplacia and not the shriveling of the skin which is of the greatest importance. He studied microscopically material from 64 cases of leucoplacia, 39 of which had cancer. Occasionally, variations were seen in the sections from the same case, but in general the picture corresponded to the stage of the disease. He describes his findings under a hyperplastic and an atrophic stage. In the former there is an extensive subepithelial leucocytic infiltration, acanthosis, and parakeratosis followed later by a marked increase in the granular layer. A considerable round cell infiltration and hyperemia are found in the connective tissue. Toward the conclusion of this stage, connective tissue and sclerosis increase. As the atrophic stage approaches, there is increasing hyperkeratosis and thickening of the granular layer but a decrease of the acanthosis and round cell infiltration in the cutis; sclerosis becomes more marked. In the typical late stage, Breisky's kraurosis, there is considerable hyperkeratosis, a thin granular layer, absence of papillæ, and atrophy of the epidermis. In the cutis, the round cell infiltration is less marked, being in circumscribed lymph zones. Mast and plasma cells are present. In many areas just beneath the epithelium, the connective tissue undergoes a peculiar collagenous change so that the upper part of the dermis has a glary appearance and contains only a few normal cells. The elastic tissue, even in the earliest stages of the disease, always showed some decrease in amount between the epithelial papillæ and directly beneath the basement membrane. This decrease became more and more marked with advance of the disease, until it was completely lost. In the lower portion of the cutis it appeared to be dislodged and disintegrated.

B. *Scleroderma circumscripta.* There are two main varieties of circumscribed scleroderma, (1) Morphea which is characterized by variously sized plaques, lines or bands which are slightly elevated or depressed and are surrounded by a violaceous or a violet tinted halo. These patches may reach the size of several inches in diameter. The central portion is usually quite hard, infil-

trated and lardaceous, and has a whitish, yellowish, or old ivory hue. (2) Card-like scleroderma of Unna and white spot disease.[1]

Through the investigations of Montgomery and Ormsby, MacKee and Wise, Wise and Rosen, and others, it is claimed, although there have been opinions to the contrary, that the cases described as white spot disease are examples of either circumscribed scleroderma or lichen planus sclerosis and that card-like scleroderma is identical with the former group. While morphea usually shows the same histology as diffuse scleroderma, a considerable variation has been met with in the card-like and white spot cases. Although some of them present histological changes in the skin similar to ordinary scleroderma, others have shown degenerative changes in the collagen and elastic tissue not commonly met with in diffuse scleroderma and morphea. Such variations, however, have been found in different lesions in the same case which has led to the belief that they represent merely steps in the evolution and development of the diseased process. The finding also of these white spots in association with diffuse scleroderma and morphea has further supported the presumed identity of the conditions.

The clinical appearance of this form of circumscribed scleroderma has been described by MacKee and Wise as follows: "White spot disease occurs mostly in females, especially in those of a neurotic temperament (according to Petges, in those with a tuberculous taint). It may occur in childhood or in early and late adult life. Most of the recorded cases were in the third or fourth decade. The disease is essentially chronic in its course, the lesions making their appearance insidiously and developing slowly. Aside from the moderate pruritus, especially in the beginning, subjective symptoms are rare. The areas of predilection are at the base of the neck, in front and behind, the upper portion of the chest and back, but the lesions may appear on the extremities, various portions of the trunk, on the genitals, etc.

"The essential lesion is a small white spot. The color may be snow-white, ivory white, mother-of-pearl, bluish-white, etc. The lesions may vary in size from a large pin-head to a dime. They may be isolated, sparse and widely scattered, or they may be numerous, grouped and confluent. The surface may be smooth or wrinkled, glistening or dull, depressed or slightly elevated, or level with the surrounding skin. There may be a raised edge and a (relatively or actually) depressed center. The entire surface of the lesion may be uniform in color and consistence, or there may be a peripheral band which is bluish, reddish, or lilac in color. Sometimes fine blood vessels may obtain at the edges. The individual spots are usually round, oval or polygonal in shape, sharply circumscribed, and having the appearance of being imbedded in the skin, like a mosaic. The integument surrounding the lesion is normal. The spots may or may not be peri-follicular; some of them may be pierced by a hair, or by several hairs; or they may contain one or more horny plugs.

"To the palpating finger, the lesions may be imperceptible, or they may impart a sense of resistance (induration), or they may feel exactly like the normal skin, or appear to be even softer than the normal skin.

"In some of the cases the lesions were somewhat scaly. In others, the superficial portion of the entire lesion could be picked out of the skin with the finger nail, disclosing a reddish-white bed beneath, sometimes showing fine blood vessels. Vigorous rubbing would detach a scale in certain instances leaving the deeper portion intact. Atrophy appeared to be a prominent feature in some of the cases. In others, nothing suggestive of atrophy could be discerned."

As previously noted, considerable variation has been met with in the histology of white spot scleroderma.[2] The collagenous tissue has usually shown hypertrophy with a more or less homogeneous or glassy appearance, degenerative changes, or sclerosis. Varying degrees of inflammatory reaction and cellular infiltration have been described. The elastic tissue has been found to be normal, decreased, or entirely absent in certain areas. The epidermis is usually atrophic with some hyperkeratosis.

Unna, in the material from his two original cases of card-like scleroderma, thought he was able to delineate histologically the various stages of evolution of the disease. In the early stage, the pathological process affected the papillary bodies and an adjacent portion of the cutis proper in the form of a sharply marginated flat patch. There was an interstitial edema, swelling up of the collagenous fibers, and the connective tissue cells were increased in number. The lymph and blood vessels were dilated and around the edge were volum-

[1] Some cases in this group have also been described as morphea guttata. Wise and Rosen in this connection express themselves as follows: "As to so called white spot disease, while it is conceded that all cases reported as such are presumably examples of guttate scleroderma, it is not, in our opinion, true that all cases of scleroderma guttata are instances of white spot disease, in the clinical sense. As stated, white spot disease deserves its individuality and its name by virtue of its dazzling white color, if for no other reason, and its non-relation to lichen sclerosis. We are under the impression that while the yellowish and pearly gray efflorescence of ordinary scleroderma guttata are relatively common, those of true white spot disease are rarely encountered."

[2] In this communication the term "white spot scleroderma" is used as a matter of convenience in referring to Unna's card-like scleroderma and the cases of white spot disease belonging in this category. We have no desire to coin a new term.

inous collections of spindle and small round cells. There was no increase or hypertrophy of the collagenous or elastic tissues. The latter was reduced in some places. In a later stage the collagenous tissue was much more homogeneous, appearing like a firm collagenous plate and the cellular infiltration had partly disappeared. The vessels were greatly narrowed and decreased in number and the elastic tissue was thin and atrophic and had disappeared in places. In a further stage of development, no cells whatever, with the exception of a few naked nuclei, were to be found in the collagenous patch; but at the border there were isolated cellular collections. The vessels had disappeared but a few groups of elastic fragments were present. The epithelio-cutis margin was broken up by irregularly formed lymph spaces.

Westberg, who first described white spot disease, reported a marked hypertrophy of the collagenous bundles which stained intensely with polychrome methylene blue assuming more of a violet than a bluish color. With Van Gieson's stain also, the staining of the affected tissue was more intense than the surrounding connective tissue and the color was more yellowish than red. The elastic tissue was preserved.

Johnston and Sherwell found that the collagen had altogether disappeared, being replaced by a granular material which had lost its characteristic acidophilic staining tendency. The elastic tissue was broken up into short lengths or granules and the network covering the papillæ had disappeared where the process was most advanced.

In Hazen's case, there was a sharply circumscribed area involving about one-half of the depth of the cutis in which the collagen had undergone marked rarefaction and degeneration with an almost complete disappearance of elastic tissue. Only a few stray cells were found in the degenerated area.

Ward examined two lesions from his case, one considered early and the other in a later stage. In the first there was an increase in the connective tissue cells and what seemed to be a new formation of young connective tissue filling up the lymph spaces. Elastic tissue was well preserved. In the older lesion there was hypertrophy of the collagenous tissue with the disappearance of the cellular infiltrate from the body of the lesion. The elastic tissue was still present but was atrophic.

Hoffmann and Juliusberg reported a uniform structure of the connective tissue in which there were elongated cells lying horizontally or forming a network. There were no thick bundles as in normal connective tissues. The subepithelial elastic tissue was absent, but a little lower down it was increased in amount. Still further down, however, at the margin of the infiltrate, it was markedly decreased and entirely absent in some areas.

Riecke found increased density of collagen with intact elastic tissue, and Petges a connective tissue thick, dense, compressed, and somewhat homogeneous.

In Kretzmer's Case 1, the connective tissue fibers were thin, stained poorly, and contained few cells. In Case 2 (clinical history of bullæ) the connective tissue was cell free with no elastica.

Montgomery and Ormsby reported 2 cases. In the first one an early small lesion showed a hypertrophic and somewhat homogeneous collagen with little tendency to interlacing of its fibers. The elastic tissue was absent or represented only by small bits here and there. In the second biopsy from the first case taken from the edge of a larger lesion, the collagen appeared as long, straight, fine bundles and fibrils with almost complete absence of elastic tissue. In the second case, the collagenous bundles were comparatively thick and hypertrophic, straighter than normal, and showed little interlacing. Elastic tissue was normal but disarranged.

MacKee and Wise studied two biopsies from their case. The first lesion showed an area of colliquative degeneration or necrosis where the tissue elements were no longer discernible. In some of the sections, a large subepidermic cavity occupied by a homogeneous mass containing a few cells was found in the center of the degenerated area. In the second biopsy, the connective tissue was dense with large, coarse, wavy fibers. The elastic tissue was present directly under the epidermis with an area beneath, however, in which it was absent or badly fragmented; lower down in the section it again appeared practically normal.

In a second case reported by Wise and Rosen, edema and swelling of the collagenous tissue was found in the early stage. Later the papillary bodies appeared as homogeneous, or occasionally granular, red staining masses with loss of staining affinity, and a notable reduction in the number of capillaries and cellular elements. The collagen in the upper part of the reticular layer showed marked alteration in places. The bundles had lost their outlines, were fragmented, giving to the whole a reticulated or mesh work appearance. The blood vessels were few in number and showed constriction of their lumina. In the terminal stage, the cutis was occupied by sclerotic bundles of collagen, poor in cellular elements. Little change was seen in the elastic tissue.

Payenneville and Cailliau report 7 cases showing variable changes in the collagenous and elastic tissues. Although some of them were quite unlike clinically, they all showed histologically a common evolution toward sclerosis.

REPORT OF CASES

CASE 1. Kraurosis and white spot scleroderma. Patient was a housewife, white, aged 51 years. She had not been particularly robust as a child, and her mother always spoke of her as the "sick one" of the family. She does not remember, however, any particular illness of importance. Her menstrual periods began at the age of 18 years, lasted about 5 days and were associated with a good deal of pain. She usually had a little whitish discharge 2 days before they appeared, but was never troubled with any chronic condition of this character. She was married at the age of 25, and a few years later had some kind of a rash which was called scarlet fever. It was mild, however, and she was confined to the house for only 2 days. Her first child was born 1 year after her marriage, dying at the age of 8 with what the doctors called "wasting disease." Three years afterward, another child was born, and the third one came 7 years later when the patient was 37 years of age. This child died at the age of 12 with "heart trouble and diabetes." Her second child is now living and well. All of her pregnancies ran a normal course, and she had no unusual trouble during confinement. Her menopause came at the age of 47. She feels that her health was moderately good during her married life until after her last child was born. At this time she began to have some pain in her side, and the lower portion of her abdomen. A suspension of the kidney, removal of the appendix and the right ovary, was done in 1921. She was then 39 years of age, and felt better for 6 or 8 months after the operation. The pain, however, returned, and it has bothered her off and on since. It was mainly for this reason that she came to the Gynecological Department of the Johns Hopkins Hospital. Her marital relations were not attended with any unusual incidents except that they precipitated attacks of itching. About 3 years ago, however, she began to have a feeling of constriction in the vagina, and since then any attempt at intercourse has been painful.

Patient's first recollection of any changes in her skin were white spots on her wrists when she was about 15 years of age. Her mother, however had apparently noticed them before and said that they were due to rheumatism. It was not until about 2 years ago, however, that her attention was called to the one on the back of the right hand, and the one on the back of the left thigh; the latter caused a little itching but the others, with the exception of those around the buttocks and genitalia, have produced no subjective symptoms.

Itching was first noticed when she was 18 years of age at the time menstruation started. Each period would be accompanied by a more or less severe pruritus which would stop promptly after menstruation ceased. The itching would at times be so intense that she would become almost frantic. The attacks continued at the same intervals after her marriage, but would also frequently follow sexual intercourse. After her last child was born, when she was 37 years of age, the itching became much less intense and did not bother her very much until about 3 years ago. At this time she began to note some soreness around her anal region, which was at times so uncomfortable when she was sitting down, that she would have to use a cushion. This was a year or more after the menopause. Pruritus became very annoying again and extended back around the anal region. She would have one or more attacks during the day and often several during the night, which disturbed her so that she could not sleep. She also had a drawing, dry feeling around the vagina and would frequently have the sensation of something coming out of the vaginal opening but seldom found anything to account for it.

Patient was first seen in the gynecological dispensary in July, 1932, and was later examined in the gastro-intestinal department. Her chief complaints then were a constant feeling of pressure in the right lower quadrant, backache, and pain in the rectum during defecation.

On examination, no important changes were found in the general physical examination. She was slightly anemic. The blood calcium was 11.1 and phosphorus 4.2 milligrams per cent. A test meal showed free hydrochloric acid, 0; total acidity, 8. X-ray examination revealed an atonic stomach, right lower quadrant adhesions, and four small stones in the gall bladder. The urine contained a trace of albumin, a few red blood cells, and many white blood cells, but in a catheterized specimen only a few white cells were present. Cultures showed Bacillus coli. Cystoscopic examination was negative with the exception that ureteral catheterization showed some obstruction in the region of the left broad ligament. The following supplementary note was made for us later through the kindness of one of the gynecologists: "The external genitalia shows numerous lesions of the skin. The labia majora are not atrophied or shrunken, but there is some loss of elasticity. The labia minora have disappeared and the clitoris can no longer be seen. There is a small urethral caruncle present. At the fourchette there is a marked area of leucoplacia, and there is some contraction of the vaginal orifice. The patient has a small rectocele. The mucous membrane over the rectocele is freely movable, and apparently the walls of the vagina show no evidence of leucoplacia or loss of subcutaneous tissue. The cervix feels normal. The uterus is of normal size and in good position. The adnexa are normal. The tissues around the posterior part of the vaginal orifice are very tender."

The patient was seen first in the skin department in July, 1932. The small labia had entirely disappeared and only a stump of the clitoris remained. (Figs. 1 and 2.) The skin on the inner surfaces of the large labia extending down over the perineum and around the anal region was dry, somewhat stiffer than normal, having a grayish or thin milk color with here and there small reddish inflamed patches and occasionally pigmented spots. Around the clitoris stump, the fourchette and in some other locations near the vaginal opening, it had the crumbly, thickened, macerated appearance characteristic of patches of leucoplacia.

In the intergluteal fold, around the perineum and the thigh folds, there were numerous pea to quarter of a dollar sized chalky white, well defined roundish or irregular patches, most of which were slightly elevated and indurated. One large patch involving most of the left side of the intergluteal fold, extended out over the crest of the buttocks; its outer edge was a little raised, scaly, wrinkled, and had a milk white color. On the other side there were numerous smaller lesions, some of them confluent. Near the anal opening the skin was somewhat pigmented, thickened and smooth, showing no definite whitish patches similar to those further out, and none of this same character could be identified on the inner surfaces of the large labia.

On the inner surfaces of both wrists, there were a dozen or more pinhead to split pea sized whitish papules similar to those around the genitalia. Some of these were slightly raised, others a little depressed or cup shaped. The surfaces were smooth or showed a few punctate depressions.

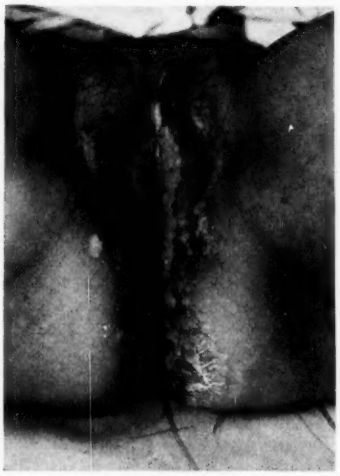


Fig. 1.

Fig. 2.

Fig. 1. Case 1. White spot scleroderma associated with changes resembling kraurosis vulvæ. The whitish papules and patches around the vulva and perineal region were definite lesions of white spot scleroderma, but we did not find the typical connective tissue changes in the specimen taken from the inner side of the large labia.

Fig. 2. Case 1. Typical lesions of white spot scleroderma on thigh and extending out over crest of the left nates.

They were round or irregular, discrete or confluent. The skin between the papules was slightly pigmented and showed some small, irregular, atrophic depressions. There were a few similar spots on the backs of the hands and on the arms, some of which were linear in shape. On the back of the right thigh, near the popliteal space, the largest of the individual lesions, with the exception of the patch on the buttocks, was found. This was about 3 centimeters in diameter, was moderately elevated, and quite scaly.

During several months that the patient was observed in the dispensary, none of the lesions ever showed any redness or other signs of inflammation, with the exception of the large patch over the left side of the buttocks and the one on the back of the right thigh. The former would often have a pinkish tint and seem to be more elevated than usual, while the latter became infected following a bruise. A superficial ulceration formed over the central portion with a surrounding redness stopping abruptly at the edge. At one section of the periphery, the epidermis was undermined by a serous, clear fluid. Under appropriate local therapy the infection healed after 2 or 3 weeks, leaving a moderately thickened, red scar showing little evidence of the original condition of the skin.

Histological examination: Four specimens of skin were taken from various locations. The tissues were fixed in Zenker's fluid to which 25 per cent of a 10 per cent formalin solution had been added. Sections stained with hematoxylin and eosin and Verhoeff's elastic tissue stain with a Van Gieson counter stain were depended upon mainly for the histological study, although various other methods were used.

Specimen 1. This included in its entirety a lesion on the arm 1 centimeter in diameter, which was smooth, white and glistening, and showed no clinical evidence of any inflammatory reaction. In the papillary layer and the upper portions of the reticular layer, a well defined area was found in which the collagenous fibers appeared to have been pulled apart with loss of substance, into interlacing, wavy fibrils, running in various directions (Figs. 3 and 4). In some locations these fibers formed a lace-like network with spaces in between, which were either clear or contained a finely granular or amorphous material. In other locations, the bundles seemed to be welded together into a more or less structureless mass. The affected portion of the cutis stained less intensely with eosin than the more normal layers beneath. Scattered among these fibrils, there were a few small, dilated capillaries and an occasional, well preserved, small round cell or larger mononuclear. The affected area gradually merged into the surrounding more normal portion of the cutis.

Elastic tissue fragments were rather numerous in the subpapillary layer of the dermis, but were completely absent in the lower portion. Around the edge of the lesion there were frequently rather large collections of cells which extended down into the fatty layer. These cells appeared to be mostly lymphocytes, but an occasional plasma cell was found. No notable changes were observed in the deeper blood vessels. Sweat glands appeared to be normal. The epidermis was atrophic with a loss of the rete pegs, and there was a moderate hyperkeratosis.

Specimen 2. This tissue was removed from the inner side of the buttocks near the perineal region. The cutis was occupied for the most part, by rather dense, fibrous tissue. Most of the bundles were fine and wavy but in one or more locations, they appeared to be hypertrophied, and had a somewhat glassy appearance. There was a rather dense cellular infiltration, particularly marked in the upper portion of the cutis which occurred in variously sized masses, as well as rows between the connective tissue bundles. These cells were mostly of the small, round type, but there was an increase in the connective tissue cells and numerous plasma cells were present, especially in the deeper layers. In one area a group of giant cells were seen which apparently surrounded the remains of a hair follicle and, in another location, there was a deposit of calcium (Fig. 5). At one end of the section, the upper portion of the cutis was occupied by a large, relatively clear space from which most of the connective tissue fibrils had disappeared. It showed a very fine reticulum containing, in most of the meshes, some fine granular material, a few cells, and some dilated capillaries. Numerous red blood cells were seen in certain areas just under the epidermis (Fig. 6). Around the border of this zone there were dense collections of cells, and the elastic tissue was compressed.

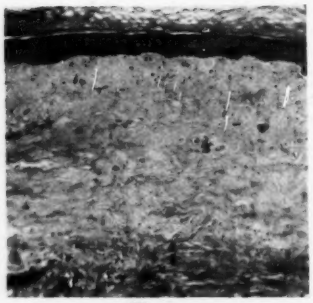


Fig. 3.

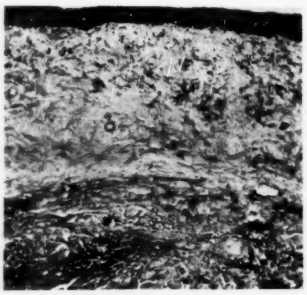


Fig. 4.

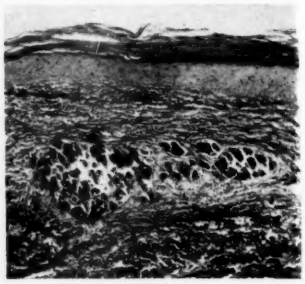


Fig. 5.

Fig. 6.

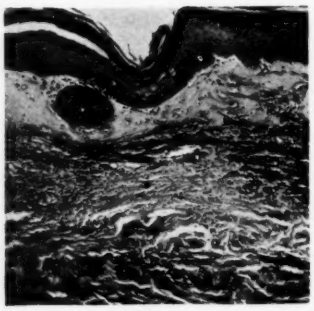


Fig. 7.

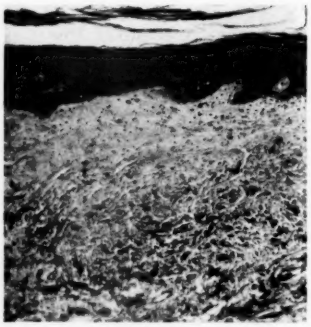


Fig. 8.

Fig. 3. Case 1. White spot scleroderma. Specimen 1. Hematoxylin and eosin stain. From a small lesion on the arm. Splitting up of collagenous bundles; decrease of connective tissue nuclei and blood capillaries.

Fig. 4. Edge of same lesion as in Figure 3. Elastic tissue stain. Note relative lack of inflammatory reaction at spreading (?) edge of papule.

Fig. 5. Case 1. White spot scleroderma. Specimen 2. Perineal region. Elastic tissue stain. Hyperkeratosis, diffuse cellular infiltration, sclerosis, and calcium deposit.

Fig. 6. Same section as in Figure 5. Hematoxylin and eosin stain. Rarefaction of connective tissue similar to that found in lesion from arm (Figs. 3 and 4).

Fig. 7. Same section as in Figure 5. Elastic tissue stain. Hyaline blocks in subpapillary zone; compression in some areas and loss in others of elastic tissue.

Fig. 8. Case 1. White spot scleroderma. Specimen 4. Inner side of large labia. Hematoxylin and eosin stain. Moderate hyperkeratosis and thickening of epidermis. No striking degenerative changes in connective tissue.

In another location the tissue immediately under the epidermis had become homogeneous, forming glassy, hyaline blocks (Fig. 7). The elastic tissue appeared dense and compressed over most of the sclerotic area, but in certain locations it was entirely absent. It had also disappeared from the clear area seen in Figure 6, and the hyaline blocks in Figure 7. The blood vessels throughout the sclerotic area were numerous and dilated but showed no important changes. Portions of hair follicles were observed here and there. The epidermis showed a loss of most of the rete pegs and was thickened in some areas. There was a considerable hyperkeratosis.

Specimen 3. This specimen was removed from the outer edge of the lesion on the left side of the buttocks. Here the entire upper part of the cutis was occupied by a relatively clear zone similar to that previously described in one portion of Section 2. Elastic tissue fragments and splintered bundles extended up into the lower portion of this area looking as if they had been pulled up by some sucking force in the upper zone. Some of the small blood vessels in the rarefied area had thickened hyaline walls. In the deeper layers, there were dense collections mainly of small round cells with, here and there, a few giant cells. The elastic fibers were disarranged and in some areas swollen and fragmented or degenerated. The epidermis was quite atrophic, but there was some hypertrophy of the horny layer, which was made up of thin, loose lamellæ.

Specimen 4. This specimen was removed from the inner side of the labia majora extending from near the stump of the clitoris over toward the outer margin. The cutis was occupied by a moderately fine, branching connective tissue which, in some areas, was rather dense and relatively poor in cells, while in others it was more loosely formed (Fig. 8). There was a scanty diffuse infiltration of cells, most of which resembled connective tissue cells, but a few lymphocytes, plasma cells, eosinophils and large mononuclears were seen. The elastic tissue had disappeared from the papillary and subpapillary portions of the cutis. The epidermis was definitely thickened, with a moderate hyperkeratosis and in some areas showed a considerable prolongation of the rete pegs.

CASE 2. White spot scleroderma. Patient was a white woman, aged 56 years. The condition had been present for 2 years. Over and underneath the breast were numerous pea to fingernail sized, roundish or elongated chalky white patches which had become confluent in certain locations (Fig. 9). Some of the lesions were a little depressed and most of them were scaly. One showed dilated capillaries on the surface, and this one was removed for histological study.

The appearance of the sections from this patient was identical with those obtained from Case 1. In some locations the same relatively clear areas (Fig. 10), with lacunæ containing degenerated red blood cells, were found as previously shown in Figure 6. Surrounding these areas, and also in certain other locations between them, the collagenous tissue had the homogeneous, wavy cell free aspect shown in Figure 3 (Fig. 11). In other sites it was of a rather dense fibrous type. The elastic tissue in the lower portion of the cutis was swollen, broken up and disarranged, often forming large twisted bundles. There were several large collections of lymphocytes with plasma cells here and there.

CASE 3. Morphea. A white woman, aged 33 years, presented a leathery smooth patch 3 by 8 centimeters over the back of the neck, which had been present for 6 months. It had a pinkish border which was surrounded by a pigmented zone. The biopsy specimen was taken through the edge of the lesion so that it contained some of the normal skin.

In the clinically normal portion of the section there were no changes, except a dilatation of the capillaries and a mild perivascular infiltration, with some increase of the pigment cells both in the cutis and the basal layer of the epidermis. As one approached the center of the section, especially in the deeper portion of the cutis, the collagenous bundles became larger and more homogeneous in appearance; there was a decrease in the blood vessels, and the connective tissue cells were compressed. Still further toward the center, the connective tissue gradually assumed a rarefied, wavy, relatively cell free appearance (Fig. 12). The elastic tissue had, for the most part, disappeared in the rarefied area, and was decreased in the papillary and subpapillary layers in most of the section. In the lower portion of the cutis, it appeared fragmented and in some areas diminished.

Fig. 9. Case 2. White spot scleroderma. Lesions on breast.

The epidermis was atrophic showing a mild hyperkeratosis over the inner portion of the section.

In the 4 other cases of morphea studied, none of the areas of rarefication of the collagenous tissue were found. This tissue showed either hypertrophy or atrophy with variable changes in the elastica, such as are more commonly met with in morphea and diffuse scleroderma.

CASE 4. Leucoplacia. Patient was a white woman, aged 64 years, who had complained of itching for 2 years. Menopause occurred 20 years ago. The external genitalia showed a loss of elasticity and subcutaneous fat, consistent with the age of the patient. The clitoris and labia majora were well defined. The labia minora were atrophic but could be identified. On the inner surfaces of the labia majora and extending to the introitus, there were well defined, white areas varying in size from 0.5 to 1 centimeter which tended to be confluent. They were slightly indurated but showed no secondary changes. The introitus was not constricted.

The section apparently was cut through the specimen across the labia majora at right angles to the vaginal opening, since on one end hair follicles and sebaceous glands

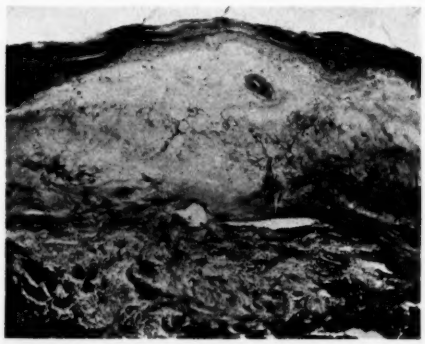


Fig. 10. Case 2. White spot scleroderma. Elastic tissue stain. Thinning out of connective tissue. Formation of lacunæ, some of which contained red blood cells. This lesion had probably been traumatized, since it was the only one in the group that showed dilated capillaries or blood spots on its surface.

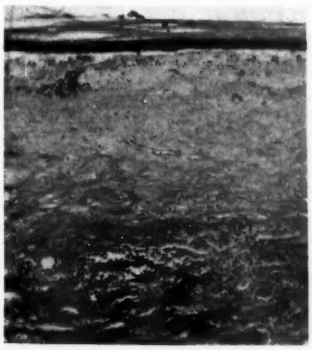


Fig. 11. Same specimen as in Figure 10. Hematoxylin and eosin stain. Does not show open spaces as seen in Figure 10, but masses of red blood cells are present in the subpapillary layer and there is a separation at the dermo-epidermal junction. Note resemblance to Figure 3 of Case 1.

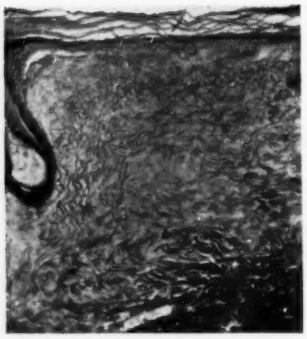


Fig. 12. Case 3. Morphea. Elastic tissue stain. Rarefaction of connective tissue and loss of elastica.

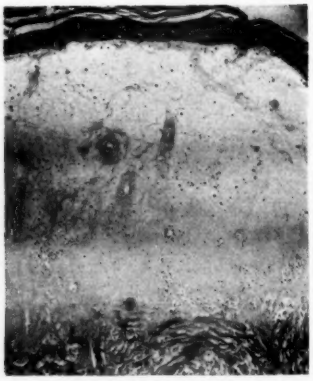


Fig. 13. Case 4. Leucoplacia. Elastic tissue stain. Marked rarefaction of connective tissue, partial preservation of small blood vessels, atrophy of epidermis.

were present. Throughout the greater portion of the cutis, the collagenous tissue had been replaced by a lightly stained homogeneous or granular substance lying in a fine reticular network (Fig. 13). Some areas were cell free, while in others both connective tissue and small round cells were quite abundant with, here and there, an occasional eosinophil and chromatophore. There were a few dilated blood vessels with well preserved walls, and just under the epidermis some spaces containing red blood cells. In one end of the sections, where the sebaceous glands and hair follicles were present, the connective tissue was quite cellular and showed some diffuse round cell infiltration. The curiously altered collagenous tissue gradually blended into the more or less normal appearing bundles in the lower half of the cutis where the blood vessels were dilated, but showed no notable changes otherwise. There was a good deal of edema and cell infiltration in the lower part of the cutis and most of the elastic tissue had disappeared. Very few elastic fibers could be seen anywhere in the papillary layer. There was a moderate degree of hyperkeratosis over most of the section, with a little thickening of the epidermis in some areas and an atrophy in others.

Case 5. Leucoplacia. Patient was a white woman, aged 60 years, who had been operated on for a carcinoma on the inner side of the labia, which was surrounded by a large area of leucoplacia. No history of itching.

Surrounding the carcinomatous area, there was a marked hypertrophy of the epidermis with an extensive thickening of the horny layer, most of whose cells contained a shriveled nucleus and many of them granules. The granular layer was quite thickened and in some areas was as wide as the rete itself. There was a rather marked diffuse cellular infiltration of the cutis and in a few locations in the subpapillary layer, the collagenous tissue was rather dense, contained few cells, and had a hyaline appearance. Very little elastic tissue was seen in the papillary and subpapillary layers. In another section taken through the lower portion of the gross specimen below the carcinoma, the connective tissue in many places was quite loose, wavy and devoid of cells. In other locations it was denser, compressed, and showed some irregularity in staining with Van Gieson. Considerable cellular infiltration was noted in various parts of the cutis. Elastic tissue had, for the most part, disappeared in the papillary and subpapillary layers. Over most of the section the epidermis was atrophic, with thickening and moderate hyperkeratosis in one or two areas.

Case 6. Leucoplacia. Patient was a white woman, aged 64 years, who had complained of itching of the vulva for 4 or 5 years. The following note was taken from the history: "The external genitalia have undergone marked changes. There is a very definite loss of subcutaneous fat. The labia minora are shrunken and the folds of the clitoris have become adherent over the clitoris so as to hide it completely. The labia majora are also shrunken, and numerous fissures are present." The gross pathological note stated that the vulva appeared normal, except for a few small, whitish patches on the skin, which were apparently leucoplacia.

Three pieces of tissue were available for study from the excised vulva. In two of these specimens, in some locations, the connective tissue in the upper half of the cutis had the same curious appearance, which has been previously described, except that it was more dense and homogeneous (Fig. 14). In other locations it was fine, loosely woven together, and diffusely infiltrated with small round cells and occasionally other types. In the lower portion, there were dense collections of lymphocytes with some plasma cells and eosinophils. Elastic tissue was absent, for the most part, in all of the specimens in the upper third of the cutis. The epidermis showed hypertrophy in a few locations but, in general, was slightly atrophic with certain irregularities in growth. In most of the sections the portion apparently nearest to the vaginal opening showed rather marked parakeratosis with a few areas of hyperkeratosis.

Case 7. Leucoplacia. (Gross microscopic note alone available). The specimen consisted of a dollar sized piece of tissue that had been removed from the upper part of the vagina, including the clitoris, which was represented by a whitish, irregular stump. Over the surface pinhead to small split pea sized, whitish spots were scattered, which were roundish, irregular or elongated in shape, with comparatively normal looking skin between. There was a definite thickening and hyperkeratosis of the tissue around and over the clitoris, and also the central portion of the specimen toward the lower border.

Two sections were taken for histological study, one across the top running through the clitoris, and the other across the lower portion of the specimen. In both sections there was a rather marked hyperkeratosis, with hypertrophy of the epidermis in some areas, but in other locations it was thin and atrophic. There was a rather diffuse cellular infiltration with many eosinophils throughout the cutis which showed marked edema, with widely dilated

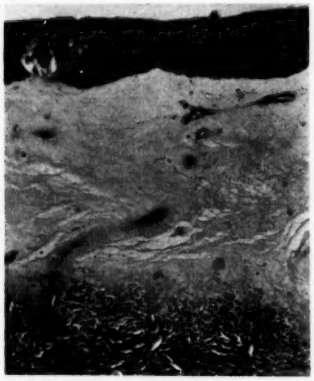


Fig. 14. Case 6. Leucoplacia. Elastic tissue stain. Homogeneous melting together of connective tissue; loss of elastica. Hyaline changes around blood vessels. Parakeratosis.

capillaries. In some locations, the connective tissue was represented by a loose network of fibrils and a homogeneous ground substance, which contained a few cells and widely dilated capillaries (Fig. 15). The elastic tissue had, for the most part, disappeared in the upper half of the cutis.

CASE 8. Leucoplacia. White woman, aged 55, had complained of itching and burning of the vulva, particularly after urination, for 8 months. She had had no previous skin trouble. Gynecological examination was negative, except for the local condition. The vulvar tissues were soft and moderately atrophic. The skin on the inner sides of the labia was red, slightly thickened, and had a dry, parched appearance. The clitoris was retracted, being represented by a navel-like pouch, and the surrounding skin had a chalky whitish appearance. In the medial line, above the clitoris and also along the midline of the perineum, there was a superficial fissure formation with some whitening of the skin around the side. The labia minora had completely disappeared, and the skin around the anus was slightly reddened. A partial vulvectomy was done, and tissue for microscopic study was taken: (1) across the fissured red area about 2 centimeters above the clitoris; (2) through a small fissure on the inner side of the vulva near the perineum; (3) across the stump of the clitoris.

In the first specimen, there was a considerable thickening of the epidermis, and a hyperkeratosis toward the center of the section which gradually decreased in amount as one approached either end. There was a dense cellular infiltration in the upper portion of the cutis most marked, also, toward the central portion of the section. The second specimen was similar to the first, but here the epidermis was somewhat more thickened except at the location of the fissure, where it had completely disappeared. In the third specimen, there was a little thickening of the epidermis, with a moderate hyperkeratosis toward the ends of the preparation, but as one approached the central part which represented the remains of the clitoris and the immediate surrounding portion, one encountered a striking homogeneous, hyaline appearance of the cutis most marked around the small blood vessels some of which were completely occluded. This area contained only a few nuclei and the overlying epidermis was atrophic (Fig. 16). The elastic tissue had disappeared, for the most part, in the upper portion of the cutis in all three preparations.

Fig. 15. Case 7. Leucoplacia. Elastic tissue stain. Rarefaction of connective tissue. Hyperkeratosis.

CASE 9. Leucoplacia. A white child aged 8, complained of pain after urination, itching of vulva, and bed-wetting, of 3 years' duration. This child had been studied in the Harriet Lange Home for some time, principally as a behavior problem. She rubbed her vulva a great deal, and one could not determine whether the primary urge was mainly itching or masturbation. Gynecological examination was negative except for the local condition.

The tissue of the vulva was soft, and there was no evidence of any diffuse sclerosis. The skin on the inner sides of both labia was thickened, and had a smooth white appearance (Fig. 17). The process involved the whole surface from the clitoris to the fourchette. There was some inflammatory reaction and maceration around the perineum and anal regions.

A section was taken through the edge of the diseased process on top of the labia. Normal appearing hair follicles and sweat glands were present throughout the entire specimen. In some areas there was a considerable thickening of the epidermis with a marked hyperkeratosis. In other locations the epidermis was atrophic with flattening out of the rete pegs. In most of the section the upper

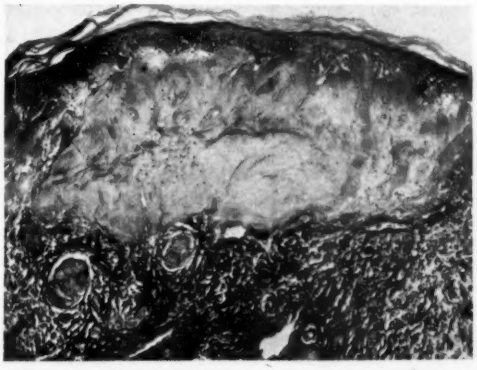


Fig. 16. Case 8. Leucoplacia. Elastic tissue stain. Homogeneous connective tissue and hyaline changes around blood vessels resembling particularly Figure 14. Atrophy of epidermis.

Fig. 17. Case 9. Leucoplacia ? of vulva in a child 8 years of age.

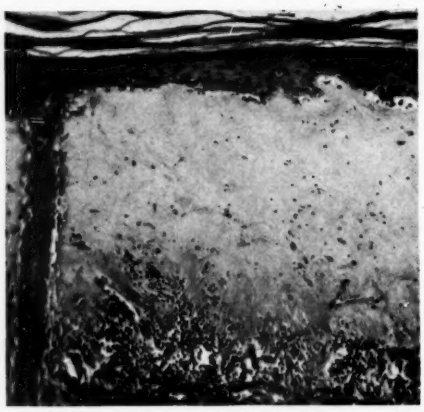


Fig. 18. Case 9. Leucoplacia ? in a child 8 years of age. Hematoxylin and eosin stain. Moderate hyperkeratosis and changes in the connective tissue similar to that found in kraurosis vulvæ and white spot scleroderma.

half of the cutis showed the same degenerated condition, which has been previously described (Fig. 18). It was most marked where the epidermis was thinnest. There was a dense, patchy, cellular infiltration along the border of the degenerated portion of the cutis, which occasionally extended down around the sweat glands and deeper structures. The cells appeared to be mostly lymphocytes and connective tissue cells, although there were some plasma cell nests in the deeper portions. In one end of the degenerated cutis there was a rather large collection of what appeared to be phagocytic monocytes.

We have reported in detail a case, Case 1, of white spot scleroderma which involved the anogenital region. It had caused, or was associated with, changes around the vulva resembling kraurosis vulvæ. Histological material from the anal region and arm showed a peculiar degeneration of the connective tissue similar to that which has been previously described in some cases of white spot scleroderma, and identical with that found in our Case 2 of this affection. Although the biopsy from the inner side of the labia did not show this change, we believe that more material would have demonstrated it, for in very few of our cases was this abnormality present throughout the entire section. It is quite apparent, also, that in lesions of white spot scleroderma situated in locations subject to trauma, the degenerated connective tissue may disappear and be replaced by sclerotic tissue. We found similar variations also in 1 of 5 cases of morphea and in 5 of 8 cases of leucoplacia of the vulva, one of which was in a child 8 years of age. We have emphasized only the connective tissue change in these affections since this was the only abnormality which we found to be particularly characteristic and, at least in our experience, unique in dermatological pathology. These changes consisted in an apparent splitting up and running together of the collagenous bundles forming a granular or more or less amorphous substance, occasionally hyaline, lying in a variably pronounced network of partly preserved connective tissue fibrils. There was also a marked diminution or complete loss of connective tissue cells and blood vessels in certain locations.

The type of cellular infiltrate, behavior of elastic tissue, secondary sclerotic changes presented no peculiarities which may not be found in other chronic inflammatory processes. The loss of elastic tissue has been emphasized in both affections. The degree of cellular infiltration and secondary sclerotic changes are apparently more marked in kraurosis vulvæ than in white spot scleroderma, but this may well be due to the increased amount of external irritation to which any lesion on the genitalia would be subjected. This point is well illustrated by comparing sections from our first biopsy taken from the arm of Case 1, with those removed from the intergluteal region (compare Figs. 3 and 4 with 5 and 7). We believe also, as have others, that this same irritative factor may be an important influence in determining the degree of epithelial thickening and hyperkeratosis, especially in kraurosis, which point is again illustrated in our Case 1 in which the lesion from the arm showed atrophy of the epidermis while those from the perineal region presented, in certain areas, a thickening and hyperkeratosis.

In our review of the histological findings of various investigators in kraurosis vulvæ and white

spot scleroderma, it will be seen that changes in the connective tissue have been described similar to those which we have emphasized. Thus, for example, in kraurosis vulvæ Gårdlund was struck by the edema and hyalinization; Peter speaks of a structureless connective tissue; Goerdes of a peculiar glistening appearance; and Taussig of a peculiar collagenous change in the dermis. Taussig's contributions are well illustrated and some of his photographs are identical in appearance with ours.

In white spot scleroderma, Unna states that the connective tissue appeared as a firm collagenous plate; Johnston and Sherwell, that it had been replaced by a granular material. Hazen found that the collagen had undergone marked rarefaction and degeneration; and McKee and Wise, speak of a colliquative degeneration or necrosis in one of their specimens.

The possibility of a relationship between kraurosis vulvæ and scleroderma was probably first advanced by Lewin in February, 1894, who, at a meeting of the Society of Gynecologists and Obstetricians in Berlin, expressed the opinion that kraurosis was a form of circumscribed scleroderma.

Peter also admits that while there are many points of similarity between these two affections, there are so many of dissimilarity that they will have to be regarded as separate entities. His histological comparison, however, was made with reference more to diffuse scleroderma than the white spot variety.

Terruhn separates kraurosis vulvæ from scleroderma because of the later loss of elastic tissue and the presence of obliterative vascular changes in the latter disease; but here again the comparison is with the histological changes more characteristic of diffuse scleroderma than the white spot form.

Frieboes denies any relationship, apparently basing his deduction mainly on clinical grounds.

The association of kraurosis vulvæ and circumscribed scleroderma in the same patient has been recorded independently by Dreuw and Breda.

As to the nature and significance of the histological changes in the connective tissue in either kraurosis or white spot scleroderma, very little is apparently known. In the former affection, however, several authors have attempted to explain, in more or less detail, the sequence of pathological events and have expressed opinions as to the immediate causes of these changes.

Gårdlund, in particular, has emphasized the edema and peculiar connective tissue changes (hyalinization), which were present in 5 of his 6 cases. He believes that the edema is a transudate because of the absence of fibrin and leucocytes, and that the reaction in the cutis is a granulation tissue stimulated by the damaged connective tissue and edema which act as foreign bodies. This granulation tissue later undergoes a fibrosis which makes more difficult the absorption of the fluid. The transudate not only fills the spaces between the collagenous bundles, but infiltrates them causing a swelling and splitting of the fibrils with some dissolution and running together. The author states that while it is most likely that all cases of kraurosis valvæ go through the stage of edema and hyalinization, he admits that it is possible for nutritional disturbances to cause a gradual sclerosis without these preliminary changes. On the other hand, Peter, whom Gårdlund says was the first to describe the edema in kraurosis vulvæ, considered it an exudate because it did contain fibrin and leucocytes; but Gårdlund also refers to publications of Trespe and Rosenstein where the edema was considered to be of inflammatory origin.

Terruhn again emphasizes the edema in the upper portion of the cutis which, he believes, leads to a pressure atrophy of the connective and elastic tissues. The connective tissue appeared swollen and homogeneous but did not entirely lose its structure and nuclei. He does not think that the hyaline changes noted by Gårdlund and Singer are important and when they do occur are secondary to the edema. He feels that the secondary reaction in the cutis is a restitution granulation tissue and not an inflammatory reaction, and that the presence of leucocytes in the rete, when they occur, is a complication due to scratching. The granulation tissue is replaced later by a sclerotic tissue.

In our own studies, we have not been able to form any well supported impressions as to the nature or significance of these connective tissue changes. It is generally agreed that the primary pathology in the various forms of scleroderma is in the connective tissue appearing at first as an hypertrophy with very little inflammatory reaction which is later followed by atrophy and sclerosis. Although white spot disease is now generally considered a variety of scleroderma, we have never seen in diffuse scleroderma or morphea, except in our Case 4, the peculiar connective tissue abnormalities which we have emphasized. Whether it is due to an interstitial edema which causes a splitting up of the collagenous fibrils and loss or running together of the colloidal cellular substance, or whether the primary pathological changes are in this colloidal substance itself

resulting in a dissolution of the fibrils, we do not know. We do feel, however, that the process is not due to simple edema, whether of the nature of a transudate or exudate, but that there is some primary fundamental disturbance in the protoplasm of the connective tissue itself. It is quite possible that the degenerated collagen could act as a foreign body and provoke a secondary restitution granulation tissue, as Terruhn believes, but in white spot scleroderma at least the lesions, when not subjected to irritation, may persist for years without showing any evidence of inflammation or secondary sclerosis.

We have made several other stains such as: Masson's trichrome, Mallory's analine blue, polychrome methylene blue, a silver stain, and some bacterial stains, besides those already enumerated. In general, the degenerated connective tissue stained in a similar manner, although often paler to the finer collagenous fibrils in the papillary bodies. Occasionally, especially around the capillaries in the affected areas, the tissues had a hyaline appearance, but we found little evidence of fibrin in the rarefied areas.

In some of our sections lacunæ or open spaces containing little or no demonstrable substance were often seen. These were due, we believe, to a tearing apart of the tissues from operative procedures or other injury. The lack of cohesiveness in these areas is well illustrated in the histological material from all of our cases, in which there was always a tendency to a separation at the epitheliocutis margin.

While it is generally conceded that white spot scleroderma is apparently a disease primarily affecting the collagenous tissue of the cutis, it is more difficult to interpret the significance of these changes in kraurosis of the vulva. Two or more possibilities may be mentioned: (1) that leucoplacia of the vulva is not a specific entity but may be the expression of various diseases modified in appearance by their location. Thus, Oppenheim states that neurodermatitis, lichen simplex chronicus, lichen planus, scleroderma, and chronic vulvitis are often thrown into the group of kraurosis vulvæ, although he believes that Breisky's kraurosis is a separate clinical entity. It seems quite likely that white spot scleroderma may affect, in some cases, only the genitalia where the individual lesions could very well intimately resemble a plaque of leucoplacia or through fusion and secondary sclerosis from irritation, Breisky's kraurosis. (2) It may be argued that the connective tissue changes characteristic of white spot scleroderma (our 2 cases at least) represent only an accidental incident in the pathology of kraurosis vulvæ. We must confess that this would have been our interpretation had we not been able to compare the histological material of Case 1 from the arm, with that around the anal region where the inflammatory reaction and secondary sclerosis were prominent features. Here, without doubt, trauma and other irritation incident to location were responsible to a considerable degree for this complication.

With reference to the whole subject we can only point out that a considerable proportion of cases classified as kraurosis vulvæ or leucoplacia are associated with peculiar connective tissue changes similar to those found in our cases of white spot scleroderma. Because of the conflicting opinions concerning the two former affections, both clinically and histologically, we believe, as expressed by Oppenheim, that several diseases involving the vulva have at times been reported as examples of kraurosis or leucoplacia. It is very likely, however, that there may be a true primary leucoplacia of the vulva in the pathological sense (marked hyperkeratosis and acanthosis) and also that the process may be secondary to other affections just as is the case, for example, in the mouth after syphilis and lichen planus. It is quite evident that many cases of whitish patches on the vulva, which have been called leucoplacia, were not a real leucoplacia in the histological sense, and in our own material only Case 4 showed a striking hypertrophy of the epidermis which was limited to the tissue immediately surrounding the carcinoma.

The frequency, however, with which cancer develops on these vulvar lesions demonstrates the strong tendency to epithelial proliferation in this location, and external irritation and a special susceptible soil are undoubtedly important contributing factors.

Our Case 9, a child 8 years old, presented clinically the picture of a diffuse leucoplacia of the vulva, although there was hardly sufficient hypertrophy of the epidermis to support this diagnosis in the histological sense. In the cutis, however, the connective tissue showed degenerative changes resembling those which were found in our cases of white spot scleroderma and leucoplacia. We have classified it temporarily with the leucoplacias in the clinical sense principally because of the location of the lesion. We have encountered nothing like it before, and Dr. Leo Brady who has had occasion to observe a great variety of gynecological affections in children especially various types of vulvitis from infection, incontinence of urine, masturbation, etc., tells us that it is unique in his experience.

CONCLUSIONS

1. Kraurosis vulvæ (leucoplacia of the vulva) shows in a considerable percentage of cases peculiar degenerative changes in the connective tissue identical in appearance with those characteristic of our cases of white spot scleroderma.

2. We believe that some cases, at least, which are diagnosed leucoplacia are examples of white spot scleroderma of the vulva. Here the characteristic degenerated collagenous bundles may be entirely replaced by secondary inflammatory and sclerotic tissue due to various local irritants. It is possible also that the vulvar tissue is peculiarly susceptible to degenerative processes in the connective tissue and that, in some cases, these changes may be only incidental to various inflammatory processes in this location.

3. Leucoplacia of the vulva (clinically whitish patches) may be produced either by degenerative processes in the connective tissue, maceration of a hyperkeratotic epidermis, or a combination of the two.

4. Leucoplacia of the vulva (histologically acanthosis and hyperkeratosis) is probably frequently superimposed on various pathological processes of the vulva whether primarily of a degenerative or inflammatory nature.

REFERENCES

1. Berkeley, C., and Bonney, V. Leucoplakic vulvitis and its relation to kraurosis vulvæ and carcinoma vulvæ. Proc. Roy. Soc. Med., 1910, 3, pt. 2: 29.
2. Breisky. Ueber Kraurosis vulvae. Ztschr. f. Heilk., 1885, 6: 69.
3. Dreuw and Breda. Quoted by MacKee and Wise and by Wise and Rosen, loc. cit.
4. Frieboes, W. Kraurosis vulvae. Dermat. Ztschr., 1929, 55: 345.
5. Gårdlund, Waldemar. Studien ueber Kraurosis vulvae unter besonderer Berucksichtigung ihrer Pathogenese und Aetiologie. Arch. f. Gynaek., 1916, 105: 317.
6. Goerdes, M. Ein Fall von Kraurosis vulva. Monatschr. f. Geburtsh. u. Gynaek., 1896, 3: 305.
7. Graves, W. P., and Smith, Van S. Kraurosis vulvae. J. Am. M. Ass., 1929, 92: 1244.
8. Hazen, H. H. An anomalous case of white spot disease. J. Am. M. Ass., 1913, 61: 393.
9. Hoffmann and Juliusberg. Quoted by MacKee and Wise and by Wise and Rosen, loc. cit.
10. Jayle F., and Bender, X. La leucoplasie de la vulva du vagin et de l'utérus. Rev. d. gynéc. et d. chir. abd., 1905, 9: 963.
11. Jayle, M. F. La sclérose vulvaire et le kraurosis vulvæ. Rev. de gynéc. et de chir. abd., 1910, 15: 604.
12. Johnston, J. C., and Sherwell, S. White spot disease. J. Cutan. Dis., 1903, 21: 302.
13. Kretzmer. Quoted by MacKee and Wise and by Wise and Rosen, loc. cit.
14. Lewin. Centralbl. f. Gynaek., 1894, 18: 311.
15. MacKee, George M., and Wise, F. White spot disease. J. Cutan. Dis., 1914, 32: 629.
16. Montgomery, F. H., and Ormsby, O. S. White spot disease. J. Cutan. Dis., 1907, 25: 1.
17. Oppenheim. Kraurosis vulvae. Handbuch der Haut und Geschlechtskrankheiten. Vol. 8 (2), p. 546. Edited by Jadossohn. Berlin, 1927.
18. Payenneville and Cailliau. Rapport entre le "white spot disease" et les sclerodermies secondaires en taches. Bull. Soc. franc. d. dermat. et syph., 1929, No. 7, 941.
19. Peter, W. Ueber Kraurosis vulvae. Monatschr. f. Geburtsh. u. Gynaek., 1896, 3: 297.
20. Riecke. Quoted by MacKee and Wise and by Wise and Rosen, loc. cit.
21. Szasz, Hugo. Ueber leukoplakische Veraenderungen der Vulva, ihre Beziehung zur Kraurosis derselben nebst zwei Faellen von Vulvocarcinom. Monatschr. f. Geburtsh. u. Gynaek., 1903, 17: 1020.
22. Taussig, F. J. Leukoplakia and cancer of the vulva. Arch. Dermat. & Syph., 1930, 21: 431; 1920, 1: 621.
23. Terruhn, E. Kraurosis vulvae. Arch. f. Gynaek., 1928, 134: 578.
24. Unna, P. G. Histopathology of the Diseases of the Skin. English translation by N. Walker, 1896.
25. Ward. Quoted by MacKee and Wise and by Wise and Rosen, loc. cit.
26. Westberg, F. Ein Fall von mit weissen Flecken einhergehender bisher nicht bekahnter Dermatose. Monatschr. f. prakt. Dermat., 1901, 33: 355.
27. Wise, F. and Rosen, I. Further observation on so called white spot disease or scleroderma circumscriptum. J. Cutan. Dis., 1917, 35: 66.

DISCUSSION

Dr. Fred Wise, New York City: To discuss this paper in a logical manner, it seems to me desirable to analyze the authors' findings first from the clinical and then from the histological aspects. They have studied and have obtained sections from cases corresponding to the clinical pictures of kraurosis vulvæ, leucoplacia and scleroderma of the anogenital region and white spot disease. Although I have encountered cases in which I hesitated to make a differential diagnosis between kraurosis and leucoplacia, I cannot recollect any instances in which the question of scleroderma, as opposed to the other two conditions, came up for serious consideration. As a matter of fact, I had always, until now, regarded the three conditions as rather well defined and usually sharply divided clinical entities, bearing in mind the frequent co-existence of kraurosis with leucoplacia of the genitals, and the tendency toward the later development of epithelioma in both. Kraurosis vulvæ was defined by Breisky as a peculiar, gradually progressive shrivelling of the external genitalia, usually appearing after the menopause, resulting eventually in a partial or complete loss of the labia minora, clitoris and labia majora, and leading to a stenosis of the introitus vaginæ. The Greek word "kraurosis" means shrinking or shrivelling. This conception naturally leads one to regard scleroderma of the anogenital region and simple leucoplacia of the vulva as diseases only remotely resembling kraurosis. However, I must admit that within the past month a patient was demonstrated with a lesion of the glans penis, in which a differential diagnosis between kraurosis and scleroderma seemed to me very difficult, although I favored the former. The case of white spot disease mentioned by the authors, which MacKee and I reported, affected the penis and scrotum and the lesions proved to be, definitely, circumscribed scleroderma. Only two instances of true scleroderma of the female anogenital region have come under my observation, but I believe that gynecologists

regard this region as a site of predilection for scleroderma, especially in elderly women. The microscopic findings described by Ketron and Ellis may prove a definite step toward the elimination of much confusion regarding kraurosis and leucoplacia, but I cannot entertain the same view with respect to scleroderma and white spot disease, when these occur on the genitalia.

While I fully appreciate the significance of their microscopic studies relating to degenerative changes in the connective tissues, in their various sections, I have the impression that the histological changes found in diffuse scleroderma, morphea and white spot disease are sufficiently definite to permit their differentiation from other diseases clinically resembling them. As to kraurosis and leucoplacia, I would hesitate to accept the idea of regarding them as one and the same disease, even in cases in which they co-exist and in which a microscopic differentiation is difficult or impossible. It is not hard to conceive that different evolutionary stages in both diseases may at times resemble one another very closely, both clinically and microscopically. It must be borne in mind that leucoplacia has a tendency to become leucokeratosis, possibly leading to cancer of the vulva, as it does in the mouth; it is true that kraurosis may also eventuate in cancer, but kraurosis is characterized by definite progressive atrophy, quite distinct from the changes peculiar to leucokeratosis with its epithelial proliferation. It appears to me that the differential diagnosis between these various conditions rests largely upon the clinician and I leave the discussion of histopathology to those with much greater experience than I possess.

Dr. Hamilton Montgomery, Rochester, Minnesota: The paper was very interesting to me because I recently made a clinical and pathological study of differentiation of kraurosis vulvæ, leucoplacic vulvitis, and pruritus vulvæ, and also because of a case that I saw recently at a dermatological meeting, which was presented as kraurosis vulvæ, but which had typical lesions of lichen sclerosus et atrophicus of Hallopeau. Furthermore, in this case there was no true atrophy or atresia of the vulva, such as one sees in kraurosis.

Cases of kraurosis, just now so well defined by Dr. Wise are to be separated from leucoplacia of the vulva and pruritus vulvæ with lichenification. Kraurosis rarely leads to epitheliomatous changes, whereas leucoplacia frequently does. It is not unusual, however, to find features of two or all three conditions superimposed in the same individual, especially as all three conditions are prone to occur in the later decades of life. The histological picture of lichen sclerosus et atrophicus and certain stages of kraurosis may be indistinguishable, but this does not necessarily denote the same etiological factors in both diseases. In both there is edema between the epidermis and cutis. The elastic tissue is not destroyed but simply frayed and splintered and separated from the papillary bodies by this edema and transudate, the latter resulting in homogenization of the connective tissue. The histological picture of the cases of morphea, including so called white spot disease, histologically present features of scleroderma and do not show the peculiar band of edema beneath the epidermis, which is the outstanding feature of lichen sclerosus and kraurosis. I am more inclined to believe that at least one, if not two, of Dr. Ketron's cases are cases of lichen sclerosus with secondary involvement of the labia and have nothing to do with true kraurosis.

Dr. Lloyd W. Ketron, Baltimore, (closing): I am disappointed that Dr. Wise has spent so much of his valuable time justifying the status of kraurosis vulvæ as a specific entity. We have taken no stand in this argument, but have used the terms more or less synonymously. One could certainly not claim that all cases of leucoplacia are examples of kraurosis vulvæ but it seems quite possible, as has been claimed by others, that the latter affection may be merely the end stage of some variety of clinical leucoplacia. As has been previously brought out, we believe that whitish patches on the vulva frequently called leucoplacia, may be produced by more than one pathological process. I am very glad to have Dr. Wise's opinion although it throws some doubt on the correctness of the diagnosis in Case 1. Although some of the lesions presented by this case are much larger than those commonly seen in white spot disease, the clinical appearance of the smaller ones certainly corresponds to this condition and the histopathology is apparently the same as that described by some investigators as characteristic of this affection. The status of white spot disease itself is too insecure to warrant a very sharp limitation of its boundaries.

With reference to the remarks of Dr. Montgomery, we certainly do not believe that the lesions, particularly on our patient's arms which have been present for many years showing very little tendency to spread, could be due to a localized edema. The fundamental process is a primary degeneration of the collagenous tissue. An infiltration of serum, however, even to the formation of bullæ, may occur when such areas are subjected to trauma. This occurred in our Case 1, in the lesions around the buttocks, but we saw nothing of this character associated with those on the arms.

TRANSDUODENAL RESECTION OF THE AMPULLA OF VATER FOR CARCINOMA OF THE DISTAL END OF THE COMMON DUCT

With Restoration of the Continuity of the Common and Pancreatic Ducts with the Duodenum[1]

VERNE C. HUNT, M.D., F.A.C.S., and JOHN W. BUDD, M.D.,[2] Los Angeles, California

THE surgical treatment of malignant tumors of the extrahepatic ducts has presented many technical difficulties. The operation of radical extirpation frequently is not applicable by virtue of the location or because of extensive involvement of the lesion; and when possible of execution, it has in the past been accompanied by a mortality rate considerably in excess of that for operable malignant disease elsewhere in the abdomen. Palliative, short-circuiting operations for malignant, obstructing lesions of the common duct have likewise been accomplished with considerable risk, but in the instances of recovery these usually have been justified by the palliation obtained.

The effect on the liver of prolonged obstructive jaundice, particularly as regards disturbance of the hepatic function and reduction of the glycogen reserve, and the effect upon the blood, particularly prolongation of the bleeding and coagulation time, are well known. These have contributed to the increased surgical risk of the jaundiced patient. However, the modern methods of pre-operative preparation of the patient with obstructive jaundice have materially reduced the risk with which surgical procedures on the biliary tract may be executed. The patients with obstruction of the terminal portion of the common duct in which the effects of prolonged obstructive jaundice are manifested are further debilitated by pancreatic insufficiency incident to obstruction of the pancreatic ducts. Lesions in the periampullary region of the duodenum producing both bile and pancreatic retention present formidable surgical problems not only in the technical execution of surgical procedures, but in the control of the various factors contributing to the surgical risk.

While malignant tumors of the extrahepatic ducts may and do occur anywhere from the hilus of the liver to the terminal portion of the common duct, Marshall and others have presented data indicating that nearly one-third of the malignant tumors of the extrahepatic ducts occur in the terminal portion of the common duct, the ampulla of Vater. The infrequency with which malignant tumors in this situation have been surgically extirpated seems to warrant recording the following case of successful transduodenal resection of the ampulla of Vater for carcinoma of the distal end of the common duct.

CASE REPORT

The patient, Mrs. M. DeR., 54 years of age, had resided in South America all her life until the past 2 years. On August 15, 1934, at the time of the original consultation, she gave a history of only 3 weeks' duration of epigastric distress and progressively deepening jaundice. The epigastric distress was associated with considerable digestive disturbance, nausea, and vomiting. There had never been any acute pain. There had been no chills but a daily temperature of 100 degrees F. The appetite was poor, and the patient had lost 10 pounds in weight during the short duration of her illness. The patient has recently had some urinary frequency, and some years ago, previous to coming to this country, she was told that she had an enlarged left kidney. At the time of the examination the patient was poorly nourished, weighed 98 pounds, and was deeply jaundiced; the systolic blood pressure was 108, diastolic 70. Examination of the head, neck, heart, lungs, and breasts was negative. Neither the liver nor gall bladder was palpable. A large cystic mass occupied the entire upper left quadrant of the abdomen, extending high under the left costal margin and posteriorly to the kidney region; it was not tender, moved with respiration, and was believed to be an enlarged left kidney, probably a left hydronephrosis. Pelvic and rectal examination was negative. There was no edema of the extremities, and all reflexes were normal.

The patient was admitted to St. Vincent's Hospital for further observation. Urinalysis: specific gravity, 1.010; acid reaction; bile, 4; no albumin, sugar, casts or pus cells but an occasional red blood cell was present. The concentration of the hemoglobin was 60 per cent, and the erythrocytes numbered 3,990,000 in each cubic millimeter of blood. Leucocytes numbered 6200 in each cubic millimeter of blood, and the differential count was as follows: lymphocytes, 36; eosinophiles, 2; basophiles, 1; neutrophiles, 60. The bleeding time was 2 minutes, 15 seconds, and the coagulation time was 4 minutes. The renal functional tests, phenolsulphonphthalein and blood urea, were within normal limits. Inasmuch as the renal functional tests were normal it seemed that abdominal exploration to determine the cause of the painless, obstructive jaundice was more important than further investigation of the urinary tract to determine the true nature of the left renal enlargement. A pre-operative diagnosis of obstructive jaundice, probably due to carcinoma of the head of the pancreas, was made.

At operation, August 17, 1934, through a high right rectus incision, it was first determined that the cystic mass occupying the left upper quadrant of the abdomen was a huge hydronephrosis of the left kidney; the right kidney was normal. The gall bladder was greatly distended and the common duct was dilated to about 2½ centimeters in diameter. The liver edge extended just below the costal

[1] Read before the Western Surgical Association, St. Louis, Missouri, December 7–8, 1934.
[2] Chief of Department of Pathology, St. Vincent's Hospital.

margin. Examination of the stomach was negative. No stones were felt in the gall bladder or common duct. Careful examination of the pancreas disclosed no tumor or abnormal consistency. Upon opening the common duct, several ounces of colorless mucoid material escaped. A finger inserted into the common duct downward toward the duodenum encountered a freely movable tumor a little more than 1 centimeter in diameter at the ampulla of Vater. The anterior wall of the duodenum was opened, exposing a non-ulcerating tumor of the ampulla projecting into the lumen of the duodenum (Fig. 1). The tumor was not adherent to the pancreas but was freely movable. A wide excision of the tumor was made, including the distal common and pancreatic ducts (Fig. 2). The pancreatic duct was about 5 millimeters in diameter (Fig. 3), and when divided liberated a considerable amount of retained pancreatic secretion. The mesial cut edges of the common and pancreatic ducts were sutured together, and the circumference of each duct was sutured to the mucosa of the posterior wall of the duodenum (Fig. 4). A short piece of catheter was loosely sutured into the pancreatic duct. After the anterior wall of the duodenum was closed, temporary external drainage of the common duct was established by a choledochostomy. The gall bladder was not drained, nor did it seem necessary to establish internal drainage of the gall bladder by any type of anastomosis.

Postoperative course: The patient's convalescence was essentially uneventful. The drainage from the choledochostomy tube remained practically colorless for 3 days, following which the bile pigment faintly appeared to become of gross normal concentration by about the eighth day, at which time the choledochostomy tube was clamped off diverting the bile into the duodenum, and bile appeared in the stool 2 days later. The choledochostomy tube was removed on the eighteenth day, which was followed immediately by complete healing without external drainage of bile. The small piece of catheter which had been loosely sutured into the pancreatic duct was passed in the stool on the tenth day. The patient was dismissed from the hospital September 15, the twenty-ninth postoperative day, at which time the jaundice had practically disappeared. The patient was presented at St. Vincent's Hospital Conference November 9, in excellent condition, having regained her normal weight.

The pathology of the tumor of the ampulla of Vater removed at operation is described by Dr. John W. Budd: The specimen is an enlarged and indurated papilla of Vater (Fig. 5), which is nipple shaped, having a base 1.2 centimeters in diameter and 0.9 centimeter in thickness, that is capped by a hemispherical dome 0.9 centimeter in diameter. The mucosa of the base and the peripheral half of the dome is intact, but surrounding the meatus of the ampulla is an eccentric zone 6 millimeters in diameter which is slightly elevated, pale, opaque, and indurated. The villi have been obliterated leaving a smooth non-ulcerated surface. The base of the specimen shows muscle of the duodenal wall, with two ducts in cross section into which small probes are readily passed, both probes appearing through a common meatus at the summit of the papilla. The ducts appear definitely dilated and the surfaces presented to inspection are covered by gray, soft nodules of tissue. A second specimen which was removed from around the ducts deeper in the duodenal wall, because the cellular tissue was visualized in the ducts close to the line of resection, showed normal structures upon subsequent microscopical examination. A horizontal section through the center of the papilla which included both ducts and the meatus was embedded in paraffin and sectioned for microscopic study (Fig. 6).

Microscopic pathology: The mucosa of the duodenal folds except for the smoothed-out portion of the dome is normal. In the latter there is complete replacement of the normal epithelial cells by neoplasm with a tubular arrangement still maintained in places but irregular branching alveoli are more numerous. This replacement is progressing centrifugally, beginning at the meatus of the ampulla. The muscle bundles in the right fold are diffusely infiltrated and broken up by neoplastic tissue which forms long branching tubules. The tumor cells are large and essentially cuboidal although giant and bizarre forms are noted. At the base of the papilla the pancreatic duct shows only a very narrow margin of normal mucosa before neoplastic epithelium is encountered on its surfaces while the common duct shows a greater margin of healthy tissue. The interval between the muscle wall of the two duodenal folds and between the base and the summit of the papilla which is normally occupied by the two ducts and the ampulla, is overgrown and almost wholly replaced by tumor with only here and there a gland yet lined by normal epithelium (Fig. 7). The tumor is a papillary type with long, narrow, branching stalks and scanty delicate stroma. The cells vary, frequently being irregular and ugly, while elsewhere there are tumor cells almost indistinguishable from the normal cells, differing only in having larger and paler nuclei with more dense cytoplasm lacking the mucous goblets. This neoplasm is interpreted as a papillary adenocarcinoma primary in the ampulla of Vater which has extended onto the duodenal surface about the meatus and into the common bile duct and pancreatic duct, and has infiltrated the fibro-muscle tissue of the duodenal wall. It has destroyed the normal structures of this region and has obstructed the ducts. Growth, as judged by the number of mitoses seen, has been quite active. Definite intravascular invasion is not demonstrated though ability of this tumor to infiltrate tissue is well shown.

INCIDENCE OF CARCINOMA IN PERIAMPULLARY REGION

Should one rely only upon the number of cases in which surgical extirpation of a malignant lesion in the periampullary region has been done, he would be inclined to the opinion that malignant disease in this situation is exceedingly uncommon. In 1927, Cohen and Colp collected from the literature only 59 cases of radical operation for carcinoma in the periampullary region of the duodenum, from 1898 to 1925, and these included 3 cases which they added. It has been possible for me to collect only 18 additional cases of radical extirpation for carcinoma of the ampulla of Vater since 1925 (including the case herein reported). The reported cases of radical extirpation of the ampulla of Vater fail to present a true idea of the incidence of malignant disease in this situation. Many more cases are recorded in which the lesion was found either to be inoperable at surgical exploration or was found at autopsy.

In 1913, Outerbridge collected 110 cases of carcinoma of the ampulla of Vater. In only 22 of these had a resection of the ampulla been done. No attempt has been made in this review to collect all of the cases of carcinoma in the periampullary region of the duodenum that have been recorded. However, search for the cases in which

radical operation has been performed has provided an opportunity for reviewing many cases in which palliative operations have been done for definitely determined malignant disease of the ampulla, or where the lesion was found at autopsy, to leave me with the impression that the cases in which radical operation was performed most conservatively represent less than 20 per cent of the cases of carcinoma in the periampullary region.

Upcott, Pallin, Einhorn and Stetten, Muller, Cohen and Colp, Busch, Fulde and others have previously presented extensive reviews of this subject. The report of Cohen and Colp provides a most complete collection of cases of radical operation for carcinoma of the ampulla in which 59 cases are listed since the first radical operation was performed by Halsted in 1898. The case reported by Abell has been deducted from Cohen and Colp's list, for it was not a radical operation for removal of the lesion, but was a case in which certain short circuiting operations were performed, and at a third and final operation transduodenal application of radium to the lesion was made. Considerable discrepancy is apparent in the collected cases published subsequent to those of Cohen and Colp. In 1927, Fulde collected 51 cases of radical operation, to which he added one of his own. He omitted 16 cases from Cohen and Colp's report (Alglave, Anschutz, Oliani, Bruett, Gohrbrandt, Muller, Tenani, Della Valle, Pozzi, 3 cases; Cohen and Colp, 3 cases; Hartman, 2 cases, also reported by Stakevitch) and added 9 not previously recorded (Brenner, Boehm, Blad, Eiselberg, 2 cases, Konjetzny, Kappis, Wrede, Fulde). Of the latter it has been possible for me to verify only those of Konjetzny and Fulde. In 1931, Muller and Rodemaker stated that 81 cases were reported in the literature. However, an analysis of this report shows the inclusion of several cases in which radical extirpation was not carried out but in which the surgical procedure consisted of a palliative short circuiting operation. In 1933, Lauwers stated there were at that time 64 cases of radical removal of a carcinoma of the ampulla of Vater recorded. Actually about 85 cases are recorded to date. Appended are the abstracts of 17 cases collected since 1925, which, with the above reported case, and in conjunction with 58 cases collected by Cohen and Colp, provide a series of 76 cases of radical resection for carcinoma in the periampullary region of the duodenum, on which this study is based. Seven of these cases are from the Mayo Clinic. Three are contained in the series collected by Cohen and Colp, 2 having been recorded by W. J. Mayo, and 1 by Renshaw, in 1922. The 4 others are appended (Judd, 2 cases; Walters, 1 case; and Pemberton, 1 case). Two cases reported by Muller and Rodemaker (Van Remynse, Van Ardenne), and 7 cases reported by Fulde (Brenner, Boehm, Blad, Eiselberg, 2 cases, Kappis, Wrede) have not been available to me.

According to Springer, periampullar carcinoma may originate in the lower end of the common bile duct, in the ampulla of Vater, the duct of Wirsung, or from the duodenal surface of the papilla of Vater. Springer quotes Rolleston in stating that one-third of all new-growths of the bile ducts arise in the lower or terminal portion of the common duct. Growths originating here are practically always carcinomas and usually progress along the course of the duct and outward into the duodenal wall, infiltrating the mucosa and finally ulcerating freely into the duodenum. Rolleston has said that carcinoma arising in the ampulla of Vater, as such, is rare. Hanot termed this lesion *cancer du pylore pancreaticobilliare* in contradistinction to neoplasm arising from the duodenal surface of the papilla or from the bile duct. It occurs as a small papillary outgrowth from the inner folds of the mucous membrane lining the ampulla. Neoplasms in the duct of Wirsung are rare. The new-growths arising from the duodenal surface of the papilla of Vater are the most common periampullar tumors and according to Springer comprise about two-thirds of all duodenal carcinomas. Murgoci has stated that the site of origin of cancer in the periampullar area is sometimes difficult to ascertain even on microscopic examination, and that observers have not all been careful to differentiate them. Practically all malignant lesions occurring in the periampullary region are carcinomas, most frequently adenocarcinoma or papillary carcinoma. Dencks, however, reported 2 cases of sarcoma, 1 of which was operated upon without success. Christopher reviewed 42 cases of benign tumor of the ampulla of Vater, 11 of which were papillomas. Case 1, that of Hansen, appended and included as carcinoma, reported as a benign papilloma at the time of excision with subsequent malignant recurrence, suggests that papilloma in this situation should be regarded as precancer if not actually malignant.

CLINICAL MANIFESTATIONS

There is nothing unusual in the age incidence of malignant disease in this situation for it corresponds with the age incidence of malignant disease elsewhere. It is of interest that the youngest patient in whom radical operation was done was 30 years of age, and that about 10 per cent of the

patients were in the fourth decade of life. The oldest patient operated upon was 66 years of age.

The clinical manifestations of malignant disease at the ampulla of Vater are those resulting from obstruction of the common bile duct and pancreatic duct, and from ulceration of the lesion with intestinal bleeding and secondary anemia. Jaundice has been a predominant clinical manifestation, intermittent or progressive, with some pain associated in approximately 50 per cent of the cases, usually not as a true biliary colic unless gall stones were present. Outerbridge, in a review of 110 cases of carcinoma in the periampullary area, found gall stones associated in only 20 per cent of the cases. While jaundice has been predominant, it has not always been present. Attention in several instances had been directed to indeterminate cause of intestinal bleeding, the source of which was found upon surgical exploration to be an ulcerating lesion of the ampulla of Vater. Diarrhea has occurred with sufficient frequency in the presence of pancreatic duct obstruction to be considered of significance, at any rate in the presence of jaundice. Denechau, et al, in discussing 6 personal cases and 17 others collected from the French literature stated that in 11 cases there was intractable diarrhea. They emphasized the diagnostic significance of indeterminate intestinal bleeding and suggested that biliary obstruction, intestinal bleeding, and intractable diarrhea may give the clue to the diagnosis of ampullary cancer.

Seldom may the clinical diagnosis of periampullar carcinoma be made, and practically always the diagnosis has been established at the time of surgical exploration or at autopsy. The diagnostic difficulties of determining the cause of obstructive jaundice are well known. Judd has stated that too much significance should not be placed on the presenting symptoms in the differential diagnosis, for he has been led to believe that painless jaundice is commonly present in cases of obstruction from stone in the common duct, and furthermore that jaundice with colic and pain is more common in cases of carcinoma of the pancreas and ducts than was formerly believed.

The frequency with which carcinoma in the periampullary region of the duodenum, producing obstructive jaundice, has been found at autopsy as a locally confined, movable, and operable lesion without extension to surrounding structures and without metastasis, urges the adoption of the rather broad policy of exploring all cases of obstructive jaundice early in the absence of definite contra-indications. In applying such a general rule it will occasionally happen that through difficulties of accurate differentiation an occasional case of non-obstructive jaundice, as proved upon exploration, will be operated upon. Such an occasional exploration is far less serious than to allow, through the adoption of a more conservative attitude, a case of obstructive jaundice caused by a surgically removable lesion to remain unexplored indefinitely.

Many have directed attention to the rapid decline of the patient with an obstructing periampullar lesion. Outerbridge stated that the average time elapsing between the onset of symptoms and death in 47 cases was 7⅓ months. In 50 per cent of the cases the duration was less than 3 months. The rapid decline of patients suffering loss of pancreatic secretion by way of an external pancreatic fistula or through pancreatic duct obstruction with pancreatic insufficiency occurring is well known. Abell has stated that cholemia and pancreatic insufficiency rapidly produce weight loss and asthenia.

SURGICAL PROCEDURES

So far as the operability of carcinoma of the periampullary region is concerned, the growth was limited to the papilla or its immediate surroundings, without glandular involvement or metastasis, and surgically removable in three-fourths of the cases reviewed by Outerbridge. Such findings were repeatedly encountered at autopsy in the cases recorded during recent years. It is noteworthy that death usually takes place before metastases occur. Shapiro and Lifvendahl studied 12 cases of carcinoma of the extrahepatic bile ducts. Metastases were present at autopsy in all cases except the 1 case in which the lesion was situated in the ampulla of Vater. A feature common to nearly all these lesions is their small size. A common finding even at early operation when jaundice is present, or at autopsy, is great distention of the gall bladder and common duct with colorless mucoid material entirely devoid of bile pigment.

Muller and Rodemaker have stated that the mortality rate of surgical procedures for carcinoma in the periampullary region ranges from 30 to 70 per cent, depending on the duration of the jaundice and the type of operation performed. From my review of the cases of carcinoma of the ampulla that have been operated upon, it may be stated that the mortality rate of palliative operations to provide internal biliary drainage by various types of anastomoses still approaches 70 per cent, while in recent years, through the employment of rather conservative methods of radical extirpation of the growth, the mortality rate of

TABLE I.—EIGHTEEN CASES OF RADICAL OPERATION FOR CARCINOMA OF THE PERI-AMPULLARY REGION OF THE DUODENUM FROM 1925–1934

Year	Surgeon	Operation performed	Result	Pathology
1922	Judd (Case 1) (Walters, 35)	1. Cholecystostomy. 2. Transduodenal excision, choledochoduodenostomy	Died 2 days after operation	Carcinoma
1923	Hansen	Transduodenal excision, cholecystostomy	Operative recovery; recurrence and death 18 mos.	1. Benign papilloma 2. Carcinoma
1925	Konjetzny	Combined transduodenal and retroduodenal excision. Reimplantation. C. D. & P. D.	Recovery	Adenocarcinoma
1925	Cabot (Potter)	Transduodenal excision. Reimplantation C. D.	Living and well 8 yrs. after operation	Carcinoma
1927	Clar	Transduodenal excision	Living and well more than 5 yrs. after operation	Papillary carcinoma
1927	Fulde	Transduodenal excision	Living and well 2 yrs. after operation	Adenocarcinoma
1928	Coller (Potter)	Transduodenal excision. Reimplantation C. D.	Died on fourth day (cholemia).	Carcinoma
1928	Busch	1. Cholecystostomy. 2. Transduodenal excision	Recovery	Adenocarcinoma
1928	Llambias	Transduodenal excision. Reimplantation C. D. & P. D.; cholecystec. & dr. C. D.	Recovery	Cylindrical cell epithelioma
1929	Dencks (Case 1)	Resection of duodenum. Reimplantation C. D. to stomach	Died on the third day. Autopsy. No metastasis	Spindle-cell sarcoma
1929	Dencks (Case 2)	Transduodenal excision. Reimplantation C. D. & P. D. Choledochostomy	Died on the sixth day postoperatively	?
1931	Walters	Transduodenal excision. Choledochoduodenostomy	Recovery	Adenocarcinoma, Grade II
1931	Pemberton (Walters)	Transduodenal excision. Lateral anastomosis C. D. & duodenum	Recurrence and death 2 yrs. after operation	Colloid carcinoma
1931	Judd (Case 2) (Walters, 34)	1. Drain gall bladder and common duct 2. Transduodenal excision	Recurrence 9 months after operation	Carcinoma
1933	Potter	Transduodenal excision. Reimplantation C. D. & P. D.	Recovery	Adenocarcinoma
1933	Lauwers (Case 1)	Transduodenal excision. Cholecyst-jejunostomy	Living and well 3 yrs. 10 mos. after operation	Cylindrical epithelioma
1933	Lauwers (Case 2)	Transduodenal excision. Cholecyst-jejunostomy	Living and well 9 months after operation	Cylindrical epithelioma
1934	Hunt	Transduodenal excision. Reimplantation C. D. & P. D. Choledochostomy	Recovery	Adenocarcinoma

resection is decreasing and approaches 30 per cent. By rather conservative methods of radical extirpation I have reference to the direct reimplantation of the common and pancreatic ducts into the duodenum instead of extensive anastomoses between the gall bladder and stomach, duodenum, or jejunum to provide internal drainage of the biliary tract. The mortality rate is materially influenced by the magnitude of the surgical procedure. Radical extirpation has been facilitated as a second stage operation in a number of instances after preliminary external drainage of the biliary tract has been established as was first successfully accomplished by W. J. Mayo. The mortality rate in general of radical extirpation of a carcinoma of the ampulla has exceeded 40 per cent. In Fulde's collected series of 52 cases of radical operation, the mortality rate was 42 per cent. In 58 cases reported by Cohen and Colp there were 25 surgical deaths, a mortality rate of 43 per cent. Of the 18 cases herein added to Cohen's and Colp's, there were but 4 surgical deaths, or a total of 29 in 76 cases, a mortality of 38 per cent for entire series.

The cases of radical extirpation herein considered were all operated upon as a one stage operation, with the exception of 8 cases, with only 2 deaths resulting from the second stage resection of the growth. This should not lead to the conclusion that the mortality rate of the two stage operation is more favorable than that of the one stage procedure, for the risk of establishing external biliary drainage or internal drainage by some type of anastomosis between the gall bladder and upper gastro-intestinal tract in the presence of obstructive jaundice is not negligible, by any means, and many patients who have been subjected to such preliminary procedures have not survived to undergo radical excision of the growth.

TABLE II.—SURGICAL PROCEDURES IN SEVENTY-SIX RADICAL OPERATIONS FOR CARCINOMA AT THE AMPULLA OF VATER

(58 Cases of Cohen and Colp and 18 herein collected)

Operation	Cases		Deaths		Per cent
Transduodenal excision	63		24		38
Transduodenal excision only		20		9	45
Transduodenal excision with reimplantation C. D. or C. D. & P. D.		19		4	21
Transduodenal excision with reimplantation C. D. or C. D. & P. D., with internal or external drainage		11		5	45.4
Transduodenal excision without reimplantation C. D. or P. D., with internal or external drainage		13		6	46
Resection duodenum	9		3		33
Retroduodenal excision	4		2		50
	76		29		38.1

Tables I and II indicate several interesting factors pertaining to mortality rate. Transduodenal excision has been the most frequent method of extirpation of the growth in the periampullary region of the duodenum. Simple transduodenal excision without regard to some disposition of the common and pancreatic ducts apparently is accompanied by approximately the same risk as the more formidable procedures which in addition to excision of the growth include cholecystostomy or choledochostomy for external drainage or the various types of anastomoses or "side tracking" operations to provide internal drainage. In some instances, the operations have been of such magnitude as to include resection of a part of the pancreas, cholecystectomy, and provisions for both internal and external drainage of the biliary tract. Transduodenal excision of the lesion with reimplantation of the common and pancreatic ducts into the posterior wall of the duodenum has apparently been carried out with the least possible risk.

Palliative operations whereby biliary obstruction is relieved by some anastomotic procedure between the gall bladder and upper gastrointestinal tract, even though executed with considerable risk, are often productive of much palliation though life may be prolonged for a matter of only a few months. Lauwers states that an anastomosis between the gall bladder and the jejunum obviates much more certainly the development of cholangitis, than where such anastomosis is made to the stomach or duodenum. In 1913, Erdman reported most excellent palliation derived from cholecystjejunostomy for carcinoma of the ampulla of Vater. Hingst's patient lived 5 years following a palliative cholecystduodenostomy.

Recurrence following radical extirpation of periampullar carcinoma has been frequent. Ten of the 47 cases that survived the operation lived less than 1 year, and in a number of other recurrences required subsequent operation for recurring jaundice or duodenal obstruction. Muller and Rodemaker's patient, despite the need of three operative procedures, lived 4 years in comparative comfort. Clar reported his case as the fourth one recorded living 5 years or more. He included those of Koerte, 17 years; Lewis, 8½ years; and Oehler, 6 years. Muller and Rodemaker stated that Koerte's case was living and well 22 years after operation. Among additional patients living 2 to 8 years after operation are those of Fulde, Cabot, Lauwers, Oliani, Tinani, Morin, and Novarro.

ABSTRACT OF SEVENTEEN CASE REPORTS OF RADICAL RESECTION OF CARCINOMA OF THE AMPULLA OF VATER, COLLECTED SINCE 1925

JUDD (personal communication, Walters, 35). The patient was a man, 55 years of age, whose complaint was upper abdominal distress of 4 months' duration, and jaundice for 2 months. Upon examination, the gall bladder was palpable, the patient was deeply jaundiced, the temperature was 101 degrees F., and the leucocyte count was 17,000. At exploration, December 27, 1921, the liver was enlarged and the gall bladder and the common duct were distended. A hard, irregular nodule was felt at the lower end of the common duct which was thought to be a carcinoma of the ampulla of Vater. A cholecystostomy was done to relieve the biliary obstruction with the idea of excising the tumor of the ampulla of Vater at a second stage operation. The gall bladder contained dark bile. The convalescence from this operation was satisfactory and the jaundice subsided and the patient gained in weight and strength. On March 24, 1922, a transduodenal resection of the ampulla of Vater was done, also a choledochoduodenostomy. The patient died March 26, 1922, 2 days after the operation. Autopsy revealed extensive hemorrhage into the gastro-intestinal tract and into the peritoneal cavity, marked atrophy of the liver, and diffuse nephritis.

Fig. 1. Tumor of ampulla of Vater visualized upon opening duodenum.

HANSEN, 1925. The patient was a man 44 years of age, who was first seen June 6, 1924. The complaint was that of jaundice, fever, vomiting of coffee ground like material, and loss of 10 kilograms in weight. The liver edge was palpable just below the costal margin and a distended gall bladder was palpable. There was bile in the urine and some blood in the stool. The pre-operative diagnosis was cancer of the pancreas, cholangitis, and probable ulcer of the duodenum near the papilla of Vater. At operation, August 15, 1924, the gall bladder was distended with colorless mucoid material, but contained no stones. There was some enlargement of the liver, but no abscess or metastases in the liver. On palpation of the duodenum a tumor was felt in the second portion, which was thought to be a tumor of the papilla of Vater. A transduodenal excision of a pigeon's-egg sized tumor was made without excision of the entire thickness of the posterior wall of the duodenum. The cut end of the common duct was seen and only a few sutures were introduced between it and the duodenal mucosa. A cholecystostomy was done. The patient made a satisfactory recovery and healing of the wound occurred without a fistula. The pathological report was benign papilloma of the papilla of Vater.

Subsequent course: The patient continued to improve for a time and regained the lost weight. Occult blood appeared in the stool and the hemoglobin dropped to 42 per cent. At the second operation, December 3, 1924 (6 months after the first operation), recurrence of the tumor at the head of the pancreas and metastases to the liver were found. A specimen removed proved to be carcinoma. The patient died 1 year later. Note: This case is included for the final diagnosis was carcinoma, even though the original report on the tumor removed was benign papilloma.

KONJETZNY, 1925. The patient was a man, 55 years of age. The history was that of cramp like pain in epigastrium and jaundice of 6 weeks' duration. The gall bladder was palpable. The diagnosis of tumor of the papilla of Vater or of the head of the pancreas was made. At operation a tumor of the ampulla of Vater was found. The duodenum was mobilized and retroduodenal division of the common duct and the pancreatic duct with resection of segment of the head of the pancreas was accomplished. A

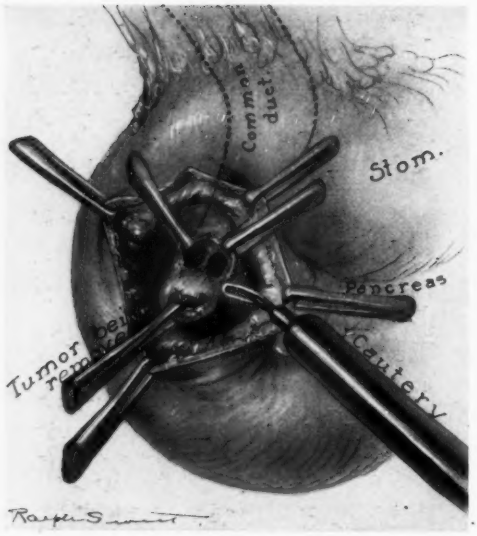


Fig. 2. Method employed in excision of tumor.

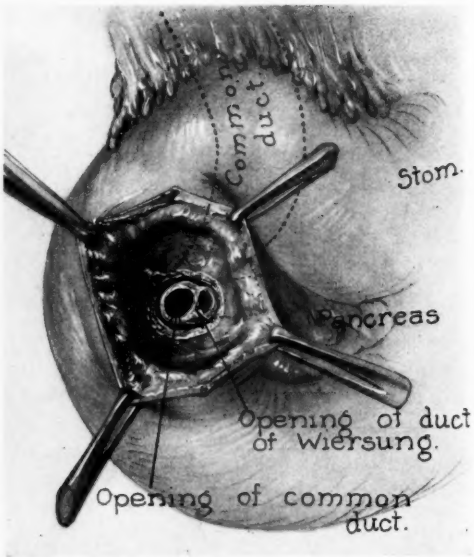


Fig. 3. Dilated common and pancreatic ducts visualized after excision of tumor.

transduodenal resection of the tumor was made and the common duct and pancreatic duct were reimplanted into the posterior wall of the duodenum. A small tube was inserted into the pancreatic duct. The patient made a satisfactory recovery. The pathological report was adenocarcinoma.

CABOT (reported by Potter). In 1925, Cabot made a transduodenal resection of the lower end of the common duct for a robin's-egg sized carcinoma, in a man 35 years of age. The common duct was reimplanted into the duodenum. Four years later cholecystectomy was done for empyema of the gall bladder, at which time the tube extending from the common duct into the duodenum was still present. In 1933, 8 years after the original operation, the patient was in good health without recurrence of jaundice. Pathology: carcinoma of the ampulla of Vater.

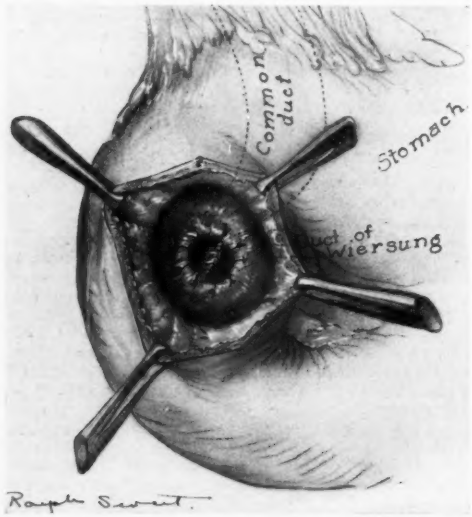


Fig. 4. Common and pancreatic ducts reimplanted into posterior wall of the duodenum.

CLAR, Fritz, 1927. The patient was a male, 50 years of age. The history was that of epigastric pain and jaundice of 5 months' duration. On physical examination the gall bladder was palpable. The pre-operative diagnosis was carcinoma of the biliary ducts. Operation, January 1, 1922. There was huge dilatation of the gall bladder and the common duct, both of which contained white bile. The biliary obstruction was found to be due to a tumor at the ampulla of Vater. A transduodenal excision of the tumor of the papilla with excision of 10 to 12 millimeters of the common duct and 5 millimeters of the pancreatic duct was made. Pathology: papillary carcinoma. Subsequent course: 4 weeks after operation the jaundice had entirely disappeared. March 3, 1927 (more than 5 years after operation), the patient was perfectly well.

FULDE, Ewald, 1927. The patient was a male, 46 years of age. The history was that of painless jaundice of 5 months' duration. On physical examination a large gall bladder was palpable. A pre-operative diagnosis of carcinoma of the liver or of the common duct was made. At operation a large distended gall bladder was found and the common duct was dilated to the size of the little finger. A tumor at the ampulla of Vater was found producing complete occlusion of the common duct. Transduodenal excision of the tumor of the ampulla was made. Pathology: adenocarcinoma. Subsequent course: the patient was living and well 2 years after operation.

COLLER (reported by Potter) did a transduodenal resection in 1928, similar to that in Cabot's case, of the common

duct in a 64 year old man. Death occurred on the fourth postoperative day from cholemia and inanition. Pathology: carcinoma.

BUSCH, 1928. The patient was a man, 54 years of age. The history was that of repeated attacks of epigastric pain referred to the right shoulder, followed by jaundice. At a first operation a cholecystostomy was done without recognition of the cause of the obstructive jaundice. Postoperative recurrent colic and jaundice led to a diagnosis of hepatitis and cholelithiasis. At the second operation by Professor Schaldemose, a tumor of the ampulla of Vater was found and a transduodenal excision of the tumor was made. Recovery occurred. Pathology: adenocarcinoma.

LLAMBIAS, 1928. The patient was a man, 42 years of age. The history was that of epigastric pain of 1 year's duration, occurring several hours after meals. There had also been some nausea and vomiting of acid like material. The stools had also on several occasions been dark. No statement was made regarding the presence of jaundice. A clinical diagnosis of gastric ulcer or cholecystitis was made. At operation, July 30, 1927, no ulcer was found, however, palpation through the anterior wall of the duodenum suggested a tumor of the second portion of the duodenum. The gall bladder, cystic and common ducts were greatly distended. A transduodenal excision of a tumor of the papilla of Vater was made and the common duct and pancreatic duct were reimplanted into the posterior wall of the duodenum. The gall bladder was removed and external drainage of the common duct was instituted. Recovery of the patient occurred. The pathological report was cylindrical cell epithelioma of the papilla of Vater.

DENCKS, Gustav, 1929. (Case 1.) The patient wa a woman, 31 years of age, who entered the clinic January 25, 1923. The history was that of upper abdominal pain, jaundice, fever, loss of appetite, and loss of weight, of 2 months' duration. The pain in the epigastrium was that of pressure. The patient was under observation for about 4 weeks at which time a pre-operative diagnosis of carcinoma of the duodenum or the pancreas was made. At operation, February 24, 1923, a small apple sized tumor was found in the region of the papilla. A resection of the duodenum including the tumor and a part of the pancreas was made with end-to-end anastomosis of the duodenum to the stomach and reimplantation of the end of the common duct into the pars pylorica. Pathology: spindle cell sarcoma. Death occurred on the third day and at autopsy no metastases were found.

DENCKS, Gustav, 1929. (Case 3.) The patient, a man, was first seen October 18, 1926. On September 5, 1926, the urine was dark colored. The next day some upper abdominal pain and jaundice were first noticed. The symptoms persisted and on February 16, 1927, a pre-operative diagnosis of obstructive jaundice due to tumor was made. At operation, February 19, 1927, a large distended gall bladder was found which contained no stones, but did contain colorless or white bile. The common duct was sufficiently dilated to allow introduction of the finger after it was opened. A tumor at the ampulla the size of a walnut was found. Transduodenal excision of the tumor was made and the common and pancreatic ducts were reimplanted into the posterior wall of the duodenum and the common duct was drained externally. Pathology of the tumor was not stated. Death occurred on the sixth day and autopsy revealed no metastases.

WALTERS, Waltman, 1931. The patient was a man, 50 years of age, whose only symptom was severe intestinal bleeding. There had been no jaundice, but for 2 weeks there had been weakness, dizziness, and shortness of breath and a weight loss of 15 pounds. Indeterminate source of intestinal bleeding led to abdominal exploration,

Fig. 5. Lateral view of resected papilla. Catgut has been passed into the common bile duct and pancreatic duct and may be seen projecting through the meatus of the ampulla. Note the zone of smooth mucosa over the apex where there is neoplastic replacement of the epithelium. ×4.

July 23, 1931. At operation palpation of the duodenum in the region of the ampulla revealed some thickening which, in conjunction with distention of the gall bladder, could not be disregarded. The duodenum was opened and an ulcerating lesion approximately 2 centimeters in diameter, involving the ampulla and the posterior wall of the duodenum, was revealed. Transduodenal resection of the entire thickness of the posterior wall of the duodenum, including the ampulla of Vater, beginning 1 centimeter beyond the periphery of the lesion and carried to the pancreas, was accomplished, and the posterior wall of the duodenum was closed. No attempt was made to isolate or identify the pancreatic duct. The common bile duct was divided above the duodenum and the proximal end was anastomosed to the duodenum over a piece of catheter. The pathological report was adenocarcinoma, graded 2, of the ampulla of Vater. The convalescence was satisfactory and on reexamination of the patient 2 months later the general condition was excellent.

PEMBERTON (reported by Walters, 34). The patient was a man, 44 years of age, whose complaint was that of stomach trouble. Following careful clinical investigation the diagnosis was indeterminate and abdominal exploration was advised. At operation October 8, 1924, a markedly distended gall bladder was found. The appendix and gall bladder were removed. There were no gall stones. The patient returned 3 months later, January, 1925, with the history that 3 weeks previously pruritis had developed, and that this had been followed by gradually deepening jaundice, without pain. At operation complete obstruction of the common bile duct, due to carcinoma of the ampulla, was found. The common duct was greatly dilated and con-

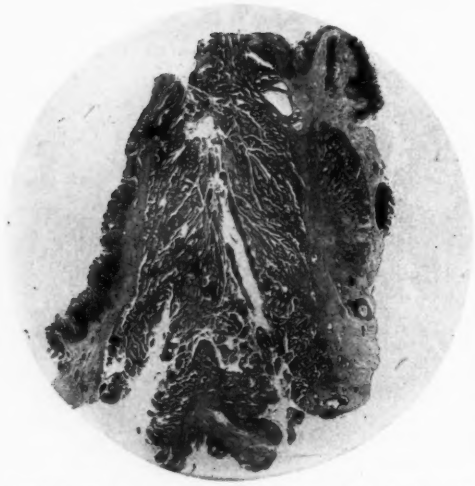


Fig. 6. Transverse section through papilla in horizontal plane (viewed from below). Note: (1) normal duodenal mucosa over the right and left folds; (2) neoplastic involvement of surface about the meatus; (3) nodule of tumor in muscle wall of right duodenal fold; (4) greatly dilated common duct (below at left) and pancreatic duct (below on right); (5) walls and surfaces of terminal ducts and ampulla and replaced by papillary tumor tissue and normal passage ways occluded. ×4.

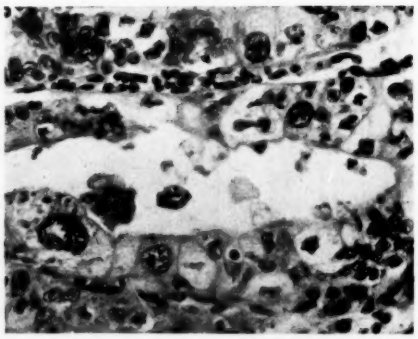


Fig. 7. Neoplastic replacement of epithelium in a gland. The tumor cells are large, varying from cuboidal to columnar in shape, usually have large vesicular nuclei and homogeneous eosinophilic cytoplasm. Degeneration and inflammation are fairly prominent here. Normal cells show smaller and more dense nuclei and the cytoplasm usually contains a mucous globule. ×300.

tained white, flocculent, mucous material. Transduodenal excision by cautery of a tumor of the papilla, 1.5 by 2.5 centimeters in diameter, was made. Lateral anastomosis was made between the common duct and the duodenum, and the cut end of the pancreatic duct was sutured to the duodenal mucosa. The pathological report was colloid carcinoma. The patient's general health remained good for 21 months, when pain developed and jaundice recurred. Exploration September 20, 1926, disclosed extensive recurrence. Death occurred in March, 1927, a little more than 2 years after extirpation of the tumor of the ampulla.

JUDD (reported by Walters, 34). The patient was a man 38 years of age, whose chief symptoms were painless jaundice, of 3½ months' duration, and loss of 47 pounds. At operation, November 1, 1928, the gall bladder and common duct were greatly dilated. A soft, movable tumor was found at the end of the common bile duct. Because of intense jaundice and the prolonged coagulation time it seemed advisable only to establish drainage which was accomplished by cholecystostomy and choledochostomy. One month later transduodenal resection of the ampulla of Vater was performed. Nine months later because of pain and recurring jaundice, abdominal exploration was carried out, which revealed a stricture or recurring carcinoma of the ampulla of Vater. Cholecystgastrostomy was performed. Seven months later a palliative gastro-enterostomy was made.

POTTER, Eugene B., 1933. The patient was a woman, 57 years of age. The history was that of epigastric pain of 3 months' duration and jaundice of 2 weeks' duration. The liver and a distended gall bladder were palpable. A preoperative diagnosis of carcinoma of the head of the pancreas was made. At operation March 6, 1933, the gall bladder was thin walled and about three times normal size and contained unconcentrated bile; the cystic and common ducts were greatly dilated, but neither the gall bladder nor ducts contained stones. Palpation through the duodenum revealed a movable, firm, hard mass, about 3.5 centimeters in diameter. The duodenum was opened and an ulcerating area involving the papilla was disclosed. The posterior wall of the duodenum with the tumor was lifted anteriorly and about 3 centimeters of the common duct was dissected free and transduodenal excision of the tumor and end of common duct with a cuff of duodenal mucous membrane 0.5 centimeter wide surrounding the ulcerated area was made. The dilated common duct and pancreatic duct were reimplanted into the posterior wall of the duodenum. Two small tubes were inserted into the common and pancreatic ducts. The patient made an uneventful recovery. Pathology: adenocarcinoma.

LAUWERS, 1933. (Case 1.) The patient was a man, 51 years of age, who was first seen at the Clinic September 18, 1929. The history of 4 months' duration, consisted of intermittent jaundice and epigastric pain accompanied by vomiting. At the time of examination the jaundice was very deep, the liver edge extended below the costal margin, but the gall bladder was not palpable. X-ray examination of the stomach was normal, however, there was interruption of the duodenal shadow at the level of the ampulla of Vater. A diagnosis of tumor of the duodenum was made. At operation, September 24, the liver was somewhat enlarged. The gall bladder was not distended and did not contain stones. Palpation of the duodenum revealed a firm mass. The duodenum was opened and a transduodenal cautery excision of an ulcerating strawberry sized tumor of the ampulla of Vater was made. A cholecystjejunostomy was made after the jejunum was divided, making the anastomosis between the gall bladder and distal end of the jejunum, implanting the proximal end of jejunum into the side of the distal jejunum. The convalescence was satisfactory and the patient was dismissed from the Clinic 3 weeks after the operation. The pathological report was cylindrical epithelioma. The patient was seen again July 8, 1933, 3 years and 10 months after operation at which time he was in good health.

LAUWERS. (Case 2.) The patient was a man 52 years of age, seen in the Clinic October 14, 1933. The symptoms

were vague epigastric pain and recent jaundice. The gall bladder was palpable. At operation October 18, 1932, the liver was considerably enlarged and the gall bladder was greatly distended but did not contain stones. Transduodenal excision of an ulcerating pea sized tumor of the ampulla of Vater was made, suturing the end of pancreatic duct to the duodenal mucosa. The common duct was dilated and a cholecystjejunostomy was made between the distal jejunum, after its division, and the gall bladder, and the proximal end of the jejunum was implanted into the distal jejunum. The pathological report was cylindrical epithelioma. The convalescence was uneventful and the patient was dismissed 17 days after operation. Nine months later, the patient was perfectly well.

The following cases have not been available for review: Brenner, Boehm, Blad, Eiselberg (2 cases), Kappis, Wrede (reported by Fulde), Van Remynse, Van Ardenne (reported by Muller and Rodemaker).

REFERENCES

1. ABELL, IRWIN. Carcinoma of the papilla of Vater. South. M. J., 1924, 17: 24–27.
2. BUSCH, E. Et Tilfaelde af Operativt Behandlet Carcinoma Papillae Vateri. Hosp.-Tid., 1928, 71: 1415–1420.
3. CABOT. Quoted by Potter.
4. CHRISTOPHER, FREDERICK. Adenoma of the ampulla of Vater. Surg., Gynec. & Obst., 1933, 56: 202–204.
5. CLAR, FRITZ. Karzinom der Papilla Vateri, excision, Heilung ueber 5 Jahre. Zentralbl. f. Chir., 1927, 54: 2119–2120.
6. COHEN, IRA, and COLP, RALPH. Cancer of the periampullary region of the duodenum. Surg., Gynec. & Obst., 1927, 45: 332–346.
7. COLLER. Quoted by Potter.
8. DENCKS, GUSTAV. Beitrag zur Diagnose und operativen Behandlung maligner Tumoren der Papilla Vateri und des Pancreas Kopfes. Deutsche Ztschr. f. Chir., 1929, 213: 147–158.
9. DENECHAU, D., TANGUY, A., and VERANGOT, P. Le Cancer de l'ampoule de Vater. Bull. méd., 1931, 45: 535.
10. EINHORN, M., and STETTEN, DEW. Carcinoma of the ampulla of Vater. Med. J. & Rec., 1924, 120: 101-106.
11. ERDMANN, J. F. Carcinoma of the papilla of Vater. Ann. Surg., 1913, 58: 687–688.
12. FULDE, EWALD. Die bekansit gewordenen Ergebnisse der Radikaloperationen de gallengangskrebse. Zentralbl. f. Chir., 1927, 54: 1481–1487.
13. HALSTED, W. B. Contributions to the surgery of the bile passages, especially the common bile duct. Johns Hopkins Hosp. Bull., 1899, 141: 645–654.
14. HANSEN, AF SVEND. Et operativt Behandlet Tilfaelde af Periampullaer Duodenalkarsinom. Ugesk. f. Læger, 1925, 35: 755–756.
15. HINGST, J. W. Een geval Van Kanker van de Papilla Vateri. Nederl. Tijdschr. v. Geneesk., Haarlem, 1926, 70: Pt. 2, 1769–1775.
16. JUDD, E. S. "Side tracking" operations in obstructive jaundice. J. Am. M. Ass., 1928, 16: 300–304.
17. KONJETZNY. Radikale Operation eines Carcinoms de Papilla vateri (einzeitige transduodenale Resektion). Klin. Wchnschr., 1925, 4: 426–427.
18. LAUWERS, E. Traitement chirurgical du cancer vatérien. J. de chir., 1933, 42: 833–842.
19. LEWIS, R. M. Cancer of the ampulla of Vater. Surg., Gynec. & Obst., 1921, 32: 543–545.
20. LLAMBIAS, J., BRACHETTO-BRIAN, D., and OROSCO, G. Contribucion al estudio de cancer de la ampulla de Vater. Semana med., 1928, 2: 649–666.
21. MARSHALL, JAMES M. Tumors of the bile ducts. Surg., Gynec. & Obst., 1932, 54: 6–12.
22. MAYO, W. J. Cancer of the common bile duct. Report of a case of carcinoma of the duodenal end of the common duct with successful excision. St. Paul M. J., 1901, 3: 374–380; Collected Papers Mayo Clinic, 1912, 1: 364–371.
23. MULLER, G. P. Carcinoma ampulla of Vater. Tr. Am. Surg. Ass., 1925, 43: 393–400.
24. MULLER, GEORGE P., and RODEMAKER, LEE. End results in radical operations for carcinoma of the periampullar region of the duodenum. Ann. Surg., 1931, 93: 755–760.
25. MURGOCI, HELEN B. Six cases of cancer arising in tissues within the duodenal loop. Bristol M.-Chir. J., 1927, 44: 195–208.
26. OUTERBRIDGE, G. W. Carcinoma of the papilla of Vater. Ann. Surg., 1913, 57: 402–426.
27. PALLIN, G. Des Carcinom des Ductus hepaticocholedochus und seine chirurgische Behandlung. (52 Schwedische Faelle.) Beitr. z. klin. Chir., 1920–1921, 121: 84–137.
28. POTTER, EUGENE B. Successful resection of the common biliary duct for carcinoma of the ampulla of Vater. Ann. Surg., 1933, 98: 369–373.
29. RENSHAW, K. Malignant neoplasms of the extrahepatic biliary ducts. Ann. Surg., 1922, 76: 205–221.
30. SHAPIRO, PHILLIP F., and LIFVENDAHL, RICHARD A. Tumors of the extrahepatic bile ducts. Ann. Surg., 1931, 94: 61–79.
31. SPRINGER, EARNEST. New growths involving the terminal bile and pancreatic ducts. Boston M. & S. J., 1925, 192: 997–1000.
32. STAKEVITCH, V. Contribution à l'etude des neoplasmes de l'ampoule de Vater. Paris, 1914.
33. UPCOTT, H. Tumors of the ampulla of Vater. Ann. Surg., 1912, 56: 710–725.
34. WALTERS, WALTMAN. Successful resection of the ampulla of Vater, including a portion of the duodenum with choledochoduodenostomy for carcinoma of the ampulla of Vater. Surg., Gynec. & Obst., 1932, 55: 648–651.
35. Idem. Personal communication.

COMPLETE EXCISION AND RECONSTRUCTION OF BOTH ACHILLES TENDONS FOR GIANT CELL XANTHOMA

FORREST YOUNG, M.D.,[1] AND C. T. HARRIS, M.D.,[1] ROCHESTER, NEW YORK

IT is not now an everyday occurrence for the surgeon to be confronted with a situation in which there is no precedent, either in the literature or in his own experience, upon which to base a plan of action. The case reported below is such a one. Tumors of tendons are so rare that some writers even doubt their existence (Buxton); we can find only one instance in which an Achilles tendon has been excised and a transplant of fascia lata made. In this case (McWhorter and Weeks) there is no mention of the end-result so that we do not know whether or not function was regained. The outcome of treatment in our patient seems to me to be of more than passing interest.

M.S. S.M.H. No. 51026. Patient was a white, married woman, aged 21 years. She first entered Strong Memorial Hospital out-patient department August 31, 1931, with a complaint of morning nausea and vomiting. She was followed for a period of 15 months in the medical and gynecological clinics. The consensus was that the cause of the morning nausea and vomiting was most likely psychic. This opinion was based on the fact that the patient wanted a child and had never become pregnant. She was admitted to the hospital on November 28, 1932, and a dilatation, curettage, and Ruben's test carried out; no cause for the sterility was found, except that the uterus was infantile in type.

During this period the patient had no complaints referable to her Achilles tendons, and numerous examinations by different observers showed the lower extremities to be normal. She was discharged on December 4, 1932.

Two weeks following discharge she returned to the gynecological clinic complaining for the first time of low backache with pain radiating down the posterior aspect of both thighs into the calves. She was referred to the orthopedic clinic where we saw her for the first time on January 27, 1933. The impression at this time was that she had a low back strain. X-ray films of the sacro-iliac joints and lower lumbar spine showed no pathological changes. She was treated with baking and massage to the back and a firm bed at home. Under this regimen the backache improved somewhat.

On February 24, 1933, she complained for the first time of pain in both Achilles tendons. Examination showed that there was thickening of both tendons with pain on dorsiflexion of the feet to 90 degrees, more marked on the left. She was treated by strapping both ankles to hold the feet in moderate plantar flexion and elevating the heels one-fourth inch. This was continued over a period of a month but afforded the patient no relief. In fact, the swelling of the tendons and the tenderness on palpation seemed to increase steadily. Her symptoms increased to such a point that she was put to bed at home for a period of 2 weeks and advised to apply external heat for a period of an hour three times a day. At the end of this time she was not improved. She now had so much pain in her heel cords on walking that it was difficult for her to get around and she walked with a shuffling limp, keeping her ankle joints as nearly fixed as possible. She was advised to enter the hospital for exploration of the tendons with a diagnosis of bilateral chronic tenosynovitis of the Achilles tendons.

She was admitted to the hospital for the second time on April 4, 1933. Complete present and past histories revealed nothing of significance except as already stated.

Physical examination showed a fairly well developed, thin girl of 22 years, who appeared chronically ill. The skin was elastic, moist, with a moderate amount of subcutaneous fat. There were no xanthomatous deposits. There was no lymphadenopathy. The head was normal. Hearing was roughly normal, with no abnormality of the external auditory canals or ear drums. The eyes and nose were normal. The mucosa of the mouth was of good color. The teeth were extremely carious. The tonsils were somewhat enlarged. There was a moderate, diffuse, non-nodular enlargement of the thyroid. The chest and breasts presented no abnormalities. The lungs were clear and the heart was normal. Abdominal examination showed no masses or palpable viscera. Pelvic examination showed uterus to be of infantile type. Reflexes were in order throughout.

Both Achilles tendons were thickened to about twice their normal width. They were extremely tender to palpation and felt rough and nodular. The involved area extended upward for about 10 centimeters from the os calcis in each tendon. Dorsiflexion of the feet was painful and voluntarily limited to about 110 degrees. The appearance of the Achilles tendons, showing their increased breadth and nodular character, can be plainly seen in Figure 1, taken April 6, 1933.

Laboratory findings: hemoglobin, 11 grams per 100 cubic centimeters; red blood cells, 4,410,000; white blood cells 6,350. Urine was cloudy, yellow, acid; specific gravity, 1.018; no albumin or sugar. Microscopic examination showed an occasional epithelial cell. The Wassermann reaction was negative. Blood cholesterol (Bloor's method) was 220 milligrams, average, on several determinations.

On the day following admission she began to complain of twinges of pain in both elbows, right shoulder, and wrist. It was thought that this might be a low grade infectious arthritis and that it and the tenosynovitis might have some relation to the infected teeth and large tonsils.

Accordingly, the upper central and lateral incisors, which showed apical infection by X-ray, were removed; and on April 14, 1933, tonsillectomy was carried out. This caused no diminution in the achillodynia whatever, although the joint symptoms disappeared.

On April 21, 1933, the left Achilles tendon was explored with the pre-operative diagnosis of chronic tenosynovitis with pain probably due to fibrous adhesions between the tendon and sheath. It was thought that freeing these might afford some relief.

Original operation: Nitrous oxide gas and ether anesthesia was used. The left lower leg was scrubbed with soap and water followed by alcohol and ether and then painted with two coats of metaphen. The limb was draped with sterile stockinette. An incision about 6 inches in length was made longitudinally and parallel to the lateral edge of the Achilles tendon from its insertion into the os calcis upward. The skin and subcutaneous tissues were divided and the edges of the wound fastened with Michel clips to the stockinette to exclude the skin from the operative field.

[1]From the Department of Surgery, Division of Orthopædics, University of Rochester School of Medicine and Dentistry

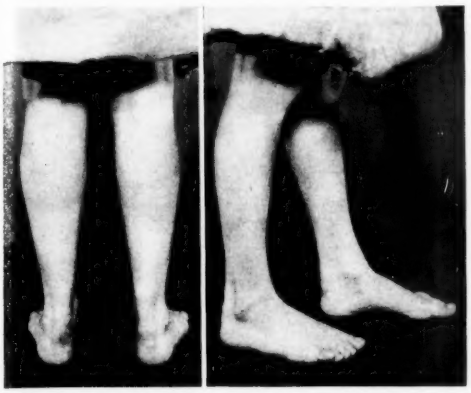


Fig. 1. External appearance of Achilles tendons, April 6, 1933, showing the increase in width and irregular contour. The nodules are quite hard and tender.

The tendon and its sheath were exposed. The sheath of the tendon had numerous ocher-yellow deposits in it. It was dissected free from the tendon which was found to be about three or four times normal size. It was irregular in contour and on palpation was nodular and hard. The tendon was incised longitudinally; as the fibers were separated, numerous hard lemon yellow nodules were seen interspersed between the tendinous fibers. This process extended from the os calcis up to within about an inch of the origin of the tendon from the muscle belly of the gastrocnemius. It was obvious that the whole process could not be removed without completely excising the tendon. It was thought that the patient's symptoms might be due to the irregularity and increase in size of the tendon. A long longitudinal wedge was removed from the tendon so that when the free edges were approximated, the tendon was approximately normal size. The subcutaneous tissues and skin were closed. Interrupted fine silk was used throughout for suture material. No immobilization was used (Fig. 2).

Following this procedure, the patient experienced considerable relief from pain on the side operated upon. The wound healed *per primam* and by the time the sutures were removed on the seventh postoperative day, motion of the left ankle was free and practically painless. We were encouraged and as the patient was continuing to complain of pain in the right tendo achillis, we decided to explore it.

Two weeks following the first operation (May 3, 1933), the right side was explored; an identical condition found and the same procedure carried out.

At the end of 10 days, the patient was up walking, although she still had pain in both tendons. She was discharged from the hospital on May 15, 1933, to be followed closely as progress of the process was to be expected, although it was thought that this would probably be slow. Figures 3 and 4 show the microscopic appearance of the tumor. In the sections one can see the tendon fibers separated by areas of invasive fibrous tissue. The connective tissue fibers are young and associated with numerous mononuclear and giant cells. The tissue is fairly vascular and resembles chronic granulation tissue. Fat stains reveal many lipochrome granules in the tumor cells. A diagnosis of giant cell xanthoma of the tendon was made.

The patient was followed at frequent intervals. She was never completely free of pain in the tendons although at

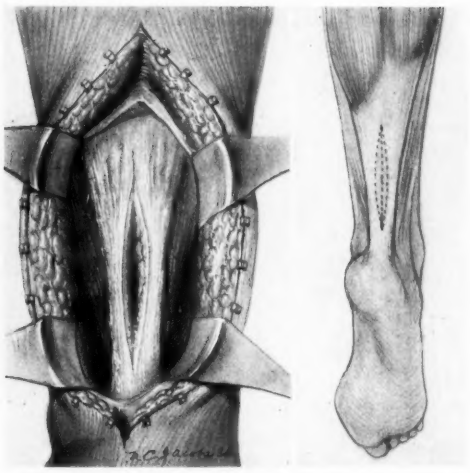


Fig. 2. Drawing of operative findings and procedure carried out April 21, 1933. The tendon was three to four times normal size and irregular in contour. Hard, lemon yellow tumor nodules are scattered between the tendinous fibers. The condition is identical bilaterally. A wedge is removed longitudinally to reduce the size of the tendon and the edges resutured. Operations on April 21, 1933, and May 3, 1933.

first this was markedly decreased in severity. Deep X-ray therapy was started on July 19, 1933, and continued until September 15, 1933, when full course of therapy had been completed. A total of 2300 units was given in divided small doses.

At the end of this time there had been no relief in symptoms; on the other hand, the tenderness and pain had increased and she was able to walk only with difficulty. She was given a period of 3 weeks to secure maximum benefit from X-ray therapy but at the end of this time no relief was in evidence. It was decided that the only hope of cure was by complete extirpation of the tendons and reconstruction of them either by tendon transplantation or fascia lata.

She was admitted to the hospital again on October 17, 1933, about 5 months following original operations. The tendons at this time were again enlarged to about three times normal size by tender indurated nodules 1 to 2 centimeters in diameter. On the left, these extended 22 centimeters upward from the os calcis and on the right, about 14 centimeters. Dorsiflexion was voluntarily limited at 110 degrees on both sides by pain in the tendons when they were stretched.

On October 18, 1933, under nitrous oxide gas and ether anesthesia, after preparation with iodine and alcohol, an incision was made along the dorsal lateral aspect of the right Achilles tendon from the os calcis to the upper third of the leg, and the skin edges were clipped to sterile stockinette. There was extensive scarring in the region of the previous operation with firm adhesions about the tendons. The tendon was excised from its calcaneal insertion to within about 8 centimeters of the lower end of the gastrocnemius muscle. All indurated tissue was removed with a wide free margin proximally. A long longitudinal incision was made on the lateral aspect of the right thigh and a

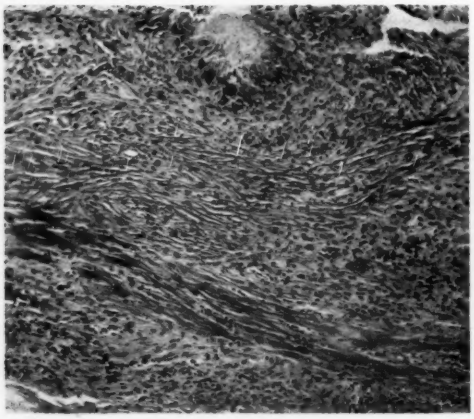


Fig. 3. Photomicrograph of the tumor tissue removed at first operation. A small area with giant cells is seen in the upper central portion of the section. Just below it are cells containing lipochrome granules; with special fat stains these cells are quite numerous and are scattered throughout the tumor. The main mass of the tissue consists of relatively young fibroblasts replacing and invading the normal tendon structure which is seen running diagonally across the lower portion of the section. ×40.

strip of fascia lata about 6 by 20 centimeters was removed. This was split at one end to form three finger like processes which were spread fanwise and sutured separately into the aponeurosis over the resected end of the gastrocnemius. The distal end of the fascia was split into two processes and these were passed through a drill hole in the os calcis and firmly united above the bone with braided silk sutures. The sural nerve was preserved throughout the dissection. The wound was closed in layers with catgut and the skin with dermal. A plaster boot was applied with the foot in marked equinus to relieve tension on the reconstructed tendon, as it was not possible to secure a strip of fascia long enough to reconstitute the tendon with the foot in neutral position. The thigh wound was closed with catgut also. Figure 5 shows the excised tendon.

The postoperative course was uneventful. On October 28, 1933, 10 days following operation, she was discharged from the hospital on crutches. During convalescence the patient continued to have severe pain in the left lower extremity. The plaster boot was left on 1 month. On removal, the wound was found to be well healed. There was about 10 degrees active flexion-extension in the ankle with midposition at about 135 degrees. The transplant felt and functioned like a normal Achilles tendon.

Massage, baking, and exercises to overcome equinus and restore motion on the right side were begun. On November 29, 1933, operation was carried out on the left side. An exactly similar process was found; the entire tendon was excised and reconstruction was carried out in the same manner as described above. The ankle was immobilized in a plaster boot with the foot in extreme equinus. The postoperative course was satisfactory.

The cast was removed at the end of a month and the wound found to be healed. Hydrotherapy, massage, and exercises were continued daily on each extremity. Progress in regaining motion and overcoming the equinus were of course slow.

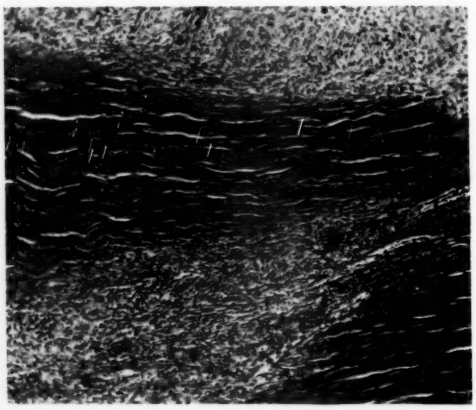


Fig. 4. This shows the normal—dark staining—fibers of the tendon being invaded by an actively growing connective tissue. ×40.

On January 20, 1934, about 8 weeks following final operation, crutch walking with partial weight-bearing was allowed. She was discharged from the hospital on March 15, 1934, able to walk for a short distance without crutches. She returned every other day for continuation of physiotherapy. Her convalescence was retarded by an acute otitis media and mastoiditis which necessitated a mastoidectomy on May 1, 1934. Following recovery from this illness, her return to activity was quite rapid. On June 8, 1934, physiotherapy was discontinued (approximately 5 months after reconstruction), as there was now a normal range of motion in both ankle joints. At this time her main difficulty seemed to be one of maintaining equilibrium and learning to walk again.

During the next 3 months she gradually learned to walk. On July 23, 1934, about 8 months following reconstruction of tendons, she was walking quite well with only a very slight limp. She was doing her own housework; had no pain in either tendo achillis region. Examination showed no evidence of recurrence of the tumor, although there was a little tenderness and induration at the calcaneal insertion of the right tendon into the os calcis.

There was a normal range of active motion in both ankle joints except for a slight limitation of dorsal flexion and the reconstructed tendons functioned as normal mechanical units. There was still only fair power of plantar flexion. She was just barely able to support her weight on her toes, but we have every reason to believe that this will rapidly improve with activity.

This patient, as one can see, presented a problem which theoretically was easy to solve but practically we had considerable trepidation in the beginning about the eventual outcome. Two procedures suggested themselves to us. The tendons evidently must be removed to relieve the patient; but how should their function be re-established? We thought of transplanting the peroneal tendons into the os calcis and arthrodesing the midtarsal and subastragalar joints to compensate for the

muscular imbalance of the foot resulting from removal of the peroneals from the lateral side of the foot. This is commonly done in gastrocnemius palsy resulting from infantile paralysis. It provides a fairly good walking foot but the peroneals never furnish the power that the gastrocnemius-soleus group has. As long as the muscle seemed to be normal it would certainly be best and simplest to reconstitute the tendon. If this failed the peroneal transplantation could be used later.

Fascia lata has of course in recent years been used to reconstruct tendons and ligaments in many parts of the body; but could it be used to replace the largest tendon in the body and withstand the strain of lifting the whole body weight with each step? The only reference to such a use in the literature is in a case reported by McWhorter and Weeks in 1925. Their patient was a 39 year old negro who had "xanthoma tuberosum multiplex." The xanthomatous deposits involved not only the Achilles tendons but the patellar, triceps, and extensor tendons of the hand. To quote from their article: "the mass from the region of the left tendo achillis was removed and a fascia transplant done. The specimen removed from the left ankle consisted of a large, circumscribed, encapsulated, and lobulated tumor mass, measuring 14 by 3.5 by 7 centimeters." There is no mention of follow-up on this patient or whether the tendon was a serviceable one.

In the original operations on this woman in which the tendons were pared down to somewhere near normal size, we again had no previous experience to guide us. But we later found an almost identical procedure had been reported by Ollerenshaw in 1923. His patient was an 18 year old girl who had hard, well defined tumors over both Achilles tendons about 2 inches above their insertions. The tumors were symmetrical and had grown slowly in size for about 3 years. She also had patches of xanthelasma on the skin of the right arm. He describes the operation as follows: "The tendon was very greatly thickened and had many yellow colored areas on its surface and also infiltrating its fibers. Certain of these patches were also present in the subcutaneous tissue. The tendon was trimmed down to a little more than its accustomed size and the skin repaired." Unlike our patient, there was no evidence of recurrence 3 years later. The microscopical sections in this case showed the typical giant and xanthoma cells.

As one can readily see these two reports while describing cases seemingly very similar to our case actually probably belong to an entirely different disease, namely, "xanthoma tuberosum multiplex." McWhorter's and Weeks' patient certainly does as the blood cholesterol by Bloor's method was 600 milligrams per 100 cubic centimeters. There are no blood cholesterol determinations reported by Ollerenshaw but the presence of xanthelasma almost surely places it in this group. If one considers the deposits in the skin and elsewhere in this systemic affection as true neoplasms, then there are a number of tumors of the Achilles tendons reported because they are one of the most common sites which the disease affects.

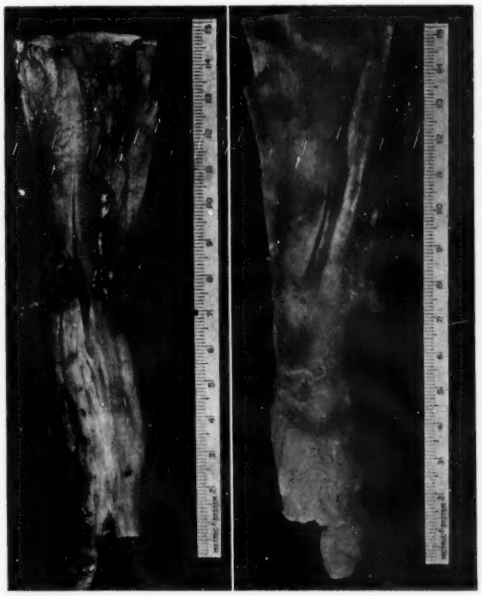


Fig. 5. The excised tendons. The specimen on the left, even in the photograph, conveys the impression of the hard, nodular character of the tumor. Notice the great size of the tendon which normally is a thin ribbon about one-half inch in width. Operations in October and November, 1933.

There has been a great deal written about "xanthoma tuberosum multiplex," the bulk of it in dermatological publications. It has been recognized as a somewhat rare clinical entity for many years. In 1882, Hutchinson tabulated 36 cases of multiple xanthoma, and in 1893, Torok reported and gave a résumé of 70 such cases. Both called attention to the fact that the manifestations of the disease were often present before puberty. Pinkus and Pick first called attention to the hypercholesterinemia practically always present in these patients. They remark that isolated xanthomas are probably true neoplasms and not associated with such a blood cholesterol increase.

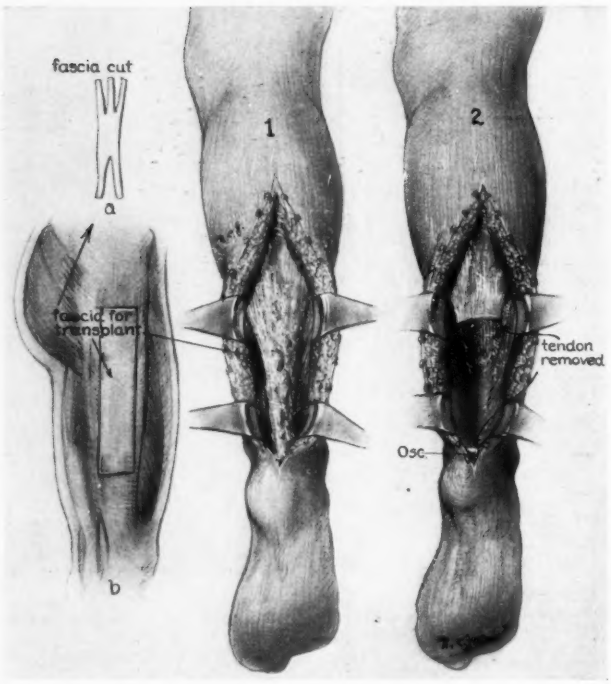


Fig. 6. Left, the tendon has been exposed throughout its entire length. The tumor extended completely down to the os calcis, but at the proximal end there was a small amount of healthy tendinous fibers to which the large fascial strip could be anchored.

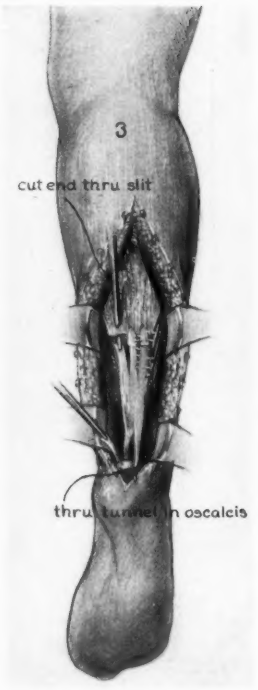


Fig. 7. The method of making the transplant. The finger like processes of either end give a strong attachment. The foot is in marked equinus for two reasons: enough length of fascia lata could not be obtained to bridge gap in neutral position, and to take strain off suture lines.

Following the discovery of hypercholesterinemia, there have been articles supporting each side of the argument. Stewart divided the growths containing foamy cells into those in which there is an elevated blood cholesterol and those without such an increase. Levy expressed the same opinion. Beeson and Albrecht reported a case with the typical distribution of the tumors over the elbows, knees, heel cords, and thumb with increased blood cholesterol. They conclude from the literature, that there is generally hypercholesterinemia in the disease. Silberberg maintains that even if it is true that imbalance of lipoid metabolism may cause a secondary xanthelasma, there are xanthomatous tumors without metabolic disturbance. Harbitz takes the half-way position. He calls attention to the fact that, in both multiple and isolated xanthomas, the tumors are located near tendons, and he believes that one cannot entirely reject the idea that the cholesterin seen in some of the isolated tumors is due to hypercholesterinemia. There is, however, a case reported of "xanthoma multiplex" in which there were no abnormal blood cholesterol values (Rosenthal and Braunisch).

On the other hand, there are those who believe that all forms of xanthoma are associated with blood cholesterol values above the normal (Weber, McWhorter, and Weeks).

From a perusal of the material written on this subject, the conclusion is almost forced on one that there are two groups of tumors which can be easily separated clinically but which, microscopically, may be indistinguishable. Both may contain giant cells, xanthoma cells, cholesterin and actively growing connective tissue or any combination of these. Clinically, there is the typical picture of "xanthoma tuberosum multiplex." In this condition there are ocher-yellow patches in the skin such as one commonly sees in the skin of the eyelids. The tumors are multiple and have a predilection for areas subjected to

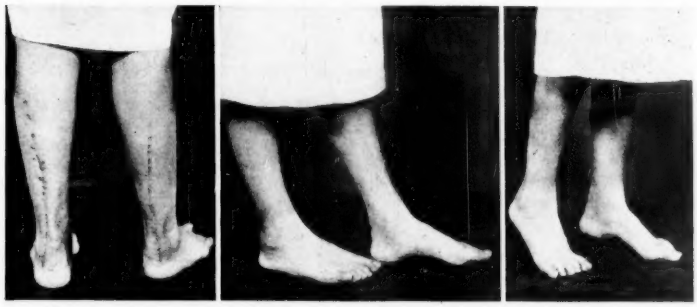


Fig. 8. The patient on September 22, 1934, approximately 1 year after operation. There is no gross evidence of recurrence as yet, although there is some tenderness and slight induration at the insertion of the right tendon into the os calcis. In the bare feet there is still slight equinus evident. In shoes this is compensated for so that the gait is practically normal. The power in the gastrocnemii is shown by the ability to support the body weight on the toes.

trauma such as the extensor surfaces of the elbows, knees, hands, and feet and are often associated with tendons, especially the Achilles tendons and the extensor tendons of the hands. The tumors do not cause any symptoms until they become so large that they mechanically interfere with function. There is practically always an increase in the blood cholesterol.

The isolated giant-cell xanthomatic tumors also present a fairly typical clinical picture. They appear as small, slowly growing, benign swellings. Trauma seems to be an important factor in the etiology. They occur most frequently on the extensor surfaces of the hands and most commonly on the index finger of the right hand (Mason and Woolston, from records of 144 cases in literature). To a lesser extent, they are seen on the dorsum of the foot and about the ankle. They practically always arise from the tendon sheaths. There is no hypercholesterinemia. Our patient belongs in this group, although there is no question that the tumor was primarily one involving the tendon itself and not the sheath, which is quite rare.

There has been a great deal written about these giant celled xanthomas of tendon sheaths since Broca reported the first case in 1860. The early literature, most of it in French, is well covered in two reviews; the first by Heurtaux in 1891 and the more recent one by Tourneux in 1913. The latter, in an extensive review, collected 93 cases of tendon sheath tumors; about 54 of these should be classed as giant celled xanthomas. Among these cases only 8 were on the lower extremities and none of these was in connection with the Achilles tendon.

The nomenclature which has been used to describe the tumors is interesting. At first they were referred to as sarcomas. But as clinical evidence accumulated, it was seen that they were essentially a benign process, even though Krogius, as late as 1922, thought that the benign view should be abandoned except for those tumors occurring on the fingers. Dor first described the xanthoma cells present in the growths and suggested the name myeloxanthoma. The English writers still refer to the tumors as giant cell myeloma or myelosarcoma.

In recent years, there have been two authors (King, 1931, and Morton of this clinic, 1934) who have suggested that the tumors of tendon sheaths probably all arise from synovial cells and would best be classified under a name suggesting this origin. King suggested the group name tenosynovioma with descriptive terms following, such as fibrous, cartilaginous, etc. Morton proposed the group of "synoviogenic tumors" to include all tumors having their origin in the synovial membranes of tendons, bursae, joint capsules, and joint linings. Under this heading, he would place the giant cell xanthoma as one of the tumors which arises from tendon sheaths. It certainly seems that the term giant cell xanthoma is the one now in most common use and probably best describes the most common of all the tumors affecting the tendons and their sheaths.

At present the main argument concerning the giant cell xanthomas is concerning whether they are neoplastic or inflammatory in nature. As noted, almost everyone who has given any thought to the subject now agrees that the isolated tumors are not associated with a systemic derangement of lipoid metabolism and that clinically they are benign and as such should be removed locally without recourse to extensive or mutilating opera-

tions. But as to whether they are neoplasms or inflammatory reactions to local irritation, there is still no general agreement.

Dor was probably the first to suggest that the tumors might be inflammatory in origin. The majority of writers before him assumed that the growth was sarcomatous, a view which is certainly not tenable at present. His views seem to be gaining ground and such writers as Fleissig, Broders, Janik, Arzt, Seyler, Kusnetzowsky, and Mason agree that the growths may well be only chronic inflammatory reactions to various irritants. Fleissig and Seyler suggest that they be called granulomas of tendon sheaths. The other viewpoint held by many writers and originally advanced by Bellamy is that the growths are endotheliomatous in nature. He applied the term myeloid endothelioma to them and his followers include Beekman, Ragins, Stewart, Gonzalez-Aguilar, and others.

Whatever the nature of the underlying process be, from a practical standpoint the important fact is that the tumors are benign, and treatment, as in other types of benign growths, should consist of local enucleation or excision. Recurrence is not an indication for amputation, but local eradication should again be carried out. In general these giant cell xanthomas should be treated in the same fashion as giant cell tumors of bone. Cases are reported in which the tumor has been removed three times before cure was effected and amputation thus avoided.

In most cases the tumor can be easily removed without the necessity of sacrificing the tendon as it is very rarely involved. But if it should be necessary to excise an important tendon, our experience indicates that fascia lata may be transplanted, will persist, and will bear as great strain as any tendon would need to undergo.

SUMMARY

Tumors of tendons are very rare. A case of isolated giant cell xanthoma tumor affecting both Achilles tendons is reported. There was no hypercholesterinemia which excludes the patient from belonging to the group of "xanthoma tuberosum multiplex." Both Achilles tendons were completely excised and new tendons reconstructed with fascia lata. Eight months following operation the reconstructed tendons are functioning as normal mechanical units.

BIBLIOGRAPHY

1. Agrifoglio, M. Contributo allo studio dei tumori delle guaine tendinee. Ann. ital. di chir., 1928, 7: 1220–1243.
2. Arzt, L. Beitraege zur Xanthom (Xanthomatosis) Frage. (C) Pseudoxanthomatose Bildungen. Arch. f. Dermat. u. Syph., 1919, 126: 907–913.
3. Beekman, F. Giant-cell tumors of the tendon sheaths. Ann. Surg., 1915, 62: 738–745.
4. Beeson, B. B., and Albrecht, P. G. A contribution to the study of xanthoma tuberosum, with report of a case. Arch. Dermat. & Syph., 1923, 8: 695–710.
5. Bellamy, H. F. The myeloid tumor of tendon sheaths. J. Path. & Bacteriol., 1901, 7: 465–480.
6. Berti, G. Contributo allo studio dei granulomi delle guaine tendinee. Tumori, 1923–1924, 10: 469–486.
7. Bonnard, A., and Chenut, A. Fibrome hemorragique. (Sarcome a myeloplaxes des gaines tendineuses.) J. de méd. de Bordeaux, 1927, 57: 489.
8. Brandao, Filho. Lipome arborescent des gaines tendineuses. Chir. d. organi di movimento, 1925, 9: 235–244.
9. Broca. Case report at meeting of the Société de Chirurgie de Paris, 1860. Bull. et mém. Soc. de chir., s.2. 1861, 1: 342.
10. Broders, A.C. Benign xanthic extraperiosteal tumor of the extremities containing foreign body giant cells. Ann. Surg., 1919, 70: 574–581.
11. Burman, M. S., and Milgram, J. E. Hæmangioma of tendon and tendon sheath. Surg., Gynec. & Obst., 1930, 50: 397–406.
12. Buxton, St. J. D. Tumours of tendon and tendon sheaths. Brit. J. Surg., 1923, 10: 469–474.
13. Cooperman, M. B. Spindle-cell sarcoma of tendon sheath; report of a case. J. Bone & Joint Surg., 1932, 14 (o. s. 30): 173–176.
14. Dor, Louis. Relations des tumeurs a myeloplaxes et des xanthomes. Cong. franç. de chir., 1898, 12: 553–562.
15. Durante, L. Sui tumori a cellule giganti delle guaine tendinee. Chir. d. organi di movimento., 1923, 7: 392–402.
16. Eisen, D. Giant-celled tumors of tendon sheaths. Am. J. Surg., 1929, 7: 120–123.
17. Ely, L. W. Giant-cell growth of bone and tendon sheath. Ann. Surg., 1918, 68: 426–428.
18. Fleissig, J. Ueber die bisher als Riesenzellensarkome (myelome) bezeichneten Granulationsgeschwulste der Sehnenscheiden. Deutsche Ztschr. f. Chir., 1913, 122: 239–265.
19. Gonzalez-Aguilar, J. Contribution to the pathogeny of tendon tumors of giant cells. J. Bone & Joint Surg., 1930, 12 (o.s. 28): 280–288.
20. Idem. Interpretacion patogenica de los tumores de mieloplaxias de los tendones. Crón. méd. mexicana, 29: 437–441.
21. Idem. Interpretacion patogenica de los tumores de mieloplaxias de los tendones. Rev. méd. de Barcelona, 1930, 13: 524–529.
22. Gorog, D. Ueber die Riesenzellengeschwulste der Sehnenscheiden. Centralbl. f. allg. Path. u. path. Anat., 1932, 53: 341–347.
23. Grant, T. P., and Stewart, M. J. On myeloid tumours of tendon sheaths, with report of a case. Glasgow M. J., 1914, 81: 333–339.
24. Harbitz, F. Tumors with xanthoma tissue. Norsk. Mag. f. Lægevidensk., 1925, 86: 321–348.
25. Idem. Tumors of tendon sheaths, joint capsules and multiple xanthoma. Arch. Path. & Lab. Med., 1927, 4: 507–527.
26. Heurtaux, M. A. Myelome des gaines tendineuses. Arch. gén. de méd., 1891, s. 7. 27: 40–54, 160–169.
27. Hutchinson, J., Sangster, A., and Crocker, H. R. Report on cases of xanthoma multiplex brought

before the Pathological Society by Mr. James Startin and Dr. Stephen Mackenzie. Tr. Path. Soc., Lond., 1882, 33: 376–384.
28. JANIK, A. Tumors of tendon sheaths. Ann. Surg., 1927, 85: 897–911.
29. JEBENS, E. H. Myeloma of tendon sheath. Proc. Roy. Soc. Med., Sect. Orthopædics, 1932, 25: 1098–1099.
30. KING, E. S. J. Concerning the pathology of tumours of tendon sheaths. Brit. J. Surg., 1931, 18: 594–617.
31. KNOWLES, F. C., and FISHER, H. N. Xanthoma tuberosum multiplex in childhood with visceral and tendon sheath involvement. J. Am. M. Ass., 1921, 77: 1557–1560.
32. KROGIUS, A. Zur Kenntnis der s. g. Xanthosarkome der Sehnenscheiden. Acta chir. Scand., 1922, 55: 363–383. Abstracted in J. Am. M. Ass., 1923, 80: 592.
33. KURTZ, A. D. Xanthoma of tendon sheath. Am. J. Surg., 1929, 7: 862–864.
34. KUSNETZOWSKY, N. J. Ein Fall multipler xanthomatoser Granulome der Sehnen. Arch. f. klin. Chir., 1923, 124: 73–80.
35. LEVY, G. Xanthelasma et xanthome. Ann. d'anat. path., 1925, 2: 247–282.
36. LEWIS, DEAN. Tumors of the tendon sheaths. Surg., Gynec. & Obst., 1934, 59: 344–349.
37. MASON, M. L., and WOOLSTON, W. H. Isolated giant cell xanthomatic tumors of the fingers and hand. Arch. Surg., 1927, 15: 499–529.
38. MCWHORTER, J. E., and WEEKS, C. Multiple xanthoma of the tendons. Surg., Gynec. & Obst., 1925, 40: 199–206.
39. MORTON, J. J. Tumors of the tendon sheaths. Surg., Gynec. & Obst., 1934, 59: 441–452.
40. OLLERENSHAW, R. Giant-celled tumours of tendon associated with xanthelasma. Brit. J. Surg., 1923, 10: 466–468.
41. PAOLUCCI, F. Sui cosiddetti tumori a mieloplassi delle guaine tendinee. Ann. ital. di chir., 1929, 8: 831–848.
42. PATEL. Osteomes developpes dans les tendons d'Achille. Lyon chir., 1931, 28: 351–352.
43. PICK and PINKUS. Weitere Mitteilung zur Lehre von den Xanthomen; die echten xanthomatosen Neubildungen. Arch. f. Dermat. u. Syph., 1910, 99: 465.
44. PINKUS and PICK. Zur Struktur und Genese der symptomatischen Xanthome. Deutsche med. Wchnschr., 1908, 34: 1426–1430.
45. PYBUS, F. C. A note on a case of myeloma of the tendon sheath. Brit. J. Surg., 1917, 5: 172–173.
46. RAGINS, A. B. Benign tumors of the tendon sheaths of unusual size. Ann. Surg., 1931, 93: 683–690.
47. ROMITI, Z. Conoscenza dei sarcomi delle guaine tendinee. Arch. ital. di chir., 1925, 12: 406–428.
48. ROSENTHAL, F., and BRAUNISCH, R. Xanthomatosis und Hypercholesterinamie. Ztschr. f. klin. Med., 1921, 92: 429–441.
49. SCAGLIOSI, F. Contributo allo studio dei tumori benigni delle guaine tendinee. Chir. d. organi di movimento., 1931, 15: 530–542.
50. SEGOVIA, J., and LLOMBART, A. Les tumores de mieloplaxias de las vainas tendinosas: estudio histologico de dos casos. Arch. de med., cirug. y especial., 1928, 28: 10–17.
51. SEYLER. Ueber xanthomatische Granulome. Arch. f. path. Anat., 1922, 239: 20–31.
52. SILBERBERG, M. Xanthome and Xanthoblastome. Arch. f. path. Anat., 1925, 254: 56–62.
53. SPIESS, P. Zur Lehre der von Sehnenscheiden und aponeurosen ausgehenden Riesenzellensarkome ("Tumeurs myeloides" und "Myelome" der Autoren). Frankfurt. Ztschr. f. Path., 1913, 13: 1–44.
54. SPRENGER, W. Zur Kenntnis der xanthomatosen Riesenzellgranulome der Sehnenscheiden. Arch. f. klin. Chir., 1932, 169: 683–687.
55. STEWART, M. J. Xanthoma and xanthosis. Brit. M. J., 1924, 2: 893–896.
56. STEWART, M. J., and FLINT, E. R. Observations on the myeloid tumour of tendon sheaths. Brit. J. Surg., 1915, 3: 90–99.
57. STRAUSS, A. Lipoma of the tendon sheaths, with report of a case and review of the literature. Surg., Gynec. & Obst., 1922, 35: 161–171.
58. TOROK, L. De la nature des xanthomes. Ann. de dermat. et de syph., 1893, s. 3., 4: 1109–1156.
59. TOURNEUX, J. P. Le diagnostic des tumeur malignes des gaines tendineuses. Progrès méd., 1920, 35: 215.
60. Idem. Les sarcomes des gaines tendineuses. Rev. de chir., 1913, 47: 817–854.
61. VALDONI, P. Lipoma arborescenta sistemico delle guaine tendinee della mano e del piede. Chir. d. organi di movimento., 1931, 15: 509–529.
62. VAN DER BEKEN, C. A propos d'un cas de tumeur a myeloplaxes des gaines tendineuses. J. de chir. et ann. Soc. belge de chir., 1932, 31–29: 27–31.
63. VASUDYVAN, A., and PAI, M. M. Benign giant cell tumors of tendon sheaths. Madras M. J., 1931, 13: 31–34.
64. WEBER, F. P. Cutaneous xanthoma and "xanthomatosis" of other parts of the body—pituitary xanthomatosis—"xanthomyelomata" of tendon-sheaths, etc.—and the "cholesterin diathesis." Brit. J. Dermatol., 1924, 36: 335–370.
65. WHITE, J. R. Arborescent lipomata of tendon sheaths; a report of two cases. Surg., Gynec. & Obst., 1924, 38: 489–490.

ACUTE INFLAMMATION OF THE PANCREAS

A Cause of Epigastric Pain in Gall-Bladder Disease and of Recurrent Pain after Cholecystectomy

ROBERT ELMAN, M.D., St. Louis, Missouri
From Department of Surgery, Washington University School of Medicine, Barnes Hospital and St. Louis City Hospital, St. Louis, Missouri

THE rôle of the pancreas in the production of symptoms in patients with gall-bladder disease, has generally been considered an infrequent and insignificant one, or has been overlooked entirely. On the other hand, the fact that patients, after removal of a diseased gall bladder, sometimes have recurrence of symptoms has disturbed surgeons even when it has not been due to a "stone left in the common duct." While it is not the purpose of this paper to present the problem of recurrent pain after cholecystectomy, it will record evidence which points to the fact that pancreatitis may be one of the reasons for its production. This data also suggests that the pancreas may be a frequent cause of symptoms even when obvious disease of the gall bladder is present. It is believed, moreover, that while such pancreatic inflammation may be a mild type of acute pancreatic necrosis, much evidence points to the fact that it is an entirely different lesion, an idea expressed several years ago by D. F. Jones. At any rate this form of acute inflammation of the pancreas was tentatively called acute interstitial pancreatitis and its relation to gall-bladder disease was suggested in a previous paper (4). Additional observations of this association will be recorded herein.

Previous Observations

Of the considerable literature on the association of pancreatic and gall-bladder disease practically all of it concerns chronic inflammation. Reports of acute pancreatic disease are confined almost entirely to cases of frank necrosis, although of course this lesion though rare is frequently associated with gall-bladder disease. The importance of acute inflammation of the pancreas without acutal necrosis (acute interstitial pancreatitis) was pointed out in the paper referred to (4) in which, of the 37 cases reviewed, it seemed probable that over half had an associated cholecystitis.

The many references in the literature to chronic pancreatitis are of value in the present study in so far as this designation represents a lesion which may be the result of repeated attacks of acute pancreatitis, an inference for which there is some evidence.

Mayo-Robson was probably the first to record the observation that he palpated an enlarged indurated pancreas during the course of a gall-bladder operation. His first case was operated on in 1890, and by 1904, 102 operations for this lesion were carried out (16). The indications for operation in the early cases (15) were "obstructive jaundice, wasting, paroxysmal attacks of pain and ague-like seizures having given rise to the suspicion of gall stones." Stones were, however, absent in half of the cases. The inference seemed justified, therefore, at least in these, that it was the pancreatic lesion which was causing the symptoms. Drainage or diversion of the bile by cholecystostomy or cholecystenterostomy (plus removal of stones where present) cured most of these patients. Follow-up studies showed that 87 were living and well; the 15 remaining either did not respond, still had symptoms of disease, or had died. The pancreatic lesion was confirmed at autopsy by microscopic examination in one or two cases and was called chronic interstitial pancreatitis. It was suggested, however, that some of these cases may have started as subacute or acute forms. In 1913, the literature was fully summarized in the monographs of Hans Kehr. This author placed the incidence of the hard indurated pancreas at 50 per cent of his cases in which operation was done and in which a stone was present in the common duct, but at only 15 per cent of cases in which stones were confined to the gall bladder. He claimed that there was nothing characteristic of the pain in patients who had pancreatitis in addition to the gall-bladder lesion in contrast to Guleke who believed, and cited 8 cases, that the localization of the pain in the mid-epigastrium with radiation to the left shoulder blade, and the back in between the shoulder blades pointed to involvement of the pancreas. Guleke pointed out, moreover, that in patients with pancreatitis the attacks were apt to be short, of 2 to 3 hours' duration, and were accompanied and followed by deep tenderness over the region of the pancreas.

Opie wrote that chronic interstitial pancreatitis "is seldom associated with such definite symptoms that it is recognizable during life and even at autopsy the condition is frequently overlooked." Nicoll, in 1919, claimed that chronic pancreatitis may simulate cholecystitis, ulcer, or appendicitis. He performed and advised biopsy of the pancreas during operation in order to establish the diagnosis through microscopic examination. In one of his cases, operated on 5 days after onset of acute symptoms (the diagnosis was intestinal obstruction or perforated ulcer) the only lesion found was an indurated pancreas surrounded by multiple areas of fat necrosis. This case is similar to others already reported (4).

There are many other records of the incidence of pancreatic lesions noted during the course of gall-bladder operations.

Judd, in 1921, for example, found 347 instances of pancreatitis among 1,200 patients operated on for gall-bladder disease (26.8 per cent). The diagnosis was based on the findings at operation, i.e. enlargement of the pancreas

especially of the head, hardness sometimes of the whole gland, lobulation, and often edema. Of the 347 cases only 38 were described in detail; 46 had stones, 8 in the common duct; in 15 the common duct was drained. Follow-up after 1 year showed 30 well (3 had attacks of diarrhea), 2 unimproved, and 16 were not heard from. Analysis of the clinical histories in the entire group of 347 cases did not reveal any special symptoms pointing to disease of the pancreas.

Of perhaps more significance is the incidence of pancreatitis in gall-bladder cases not relieved by cholecystectomy.

The most complete study of recurrent pain after cholecystectomy was written by Talman. Although pancreatitis was discussed as one of the prominent causes, he recorded the general belief that there was nothing characteristic in the clinical picture of those cases of gall-bladder disease which at operation also disclosed pancreatitis. However, he also called attention to the inaccuracy of a diagnosis of pancreatic involvement based merely on palpation at operation. This was apparent from the variable incidence of the lesion as reported by many surgeons; figures between 9 and 81 per cent were found of the frequency of pancreatic disease in gall-bladder cases. The error, of course, may be in both directions, i.e. definite pancreatitis may be missed and the gland reported normal or an enlarged head described due to a thick fatty mesentery through which a normal gland is felt. Nicoll believed that actual biopsy of the gland is necessary to make a diagnosis. Certainly inspection or palpation of the visible gland should increase considerably its accuracy.

Douglas recently reported a number of cases, 3 of which "after cholecystectomy for cholelithiasis had epigastric or left hypochondric pain of varying degrees, which was believed by the operator to have been mild attacks of pancreatitis." In another patient operation revealed a hard indurated pancreas, fat necrosis, and stones in the gall bladder. Recurrent pain occurred 3 weeks after operation but the pain disappeared after the re-establishment of bile drainage.

Present Observations

In all, 6 cases will be described; in 5 of them the evidence of pancreatitis is anatomically conclusive, in the other one merely presumptive. The clinical histories are given. Table I summarizes the most important findings.

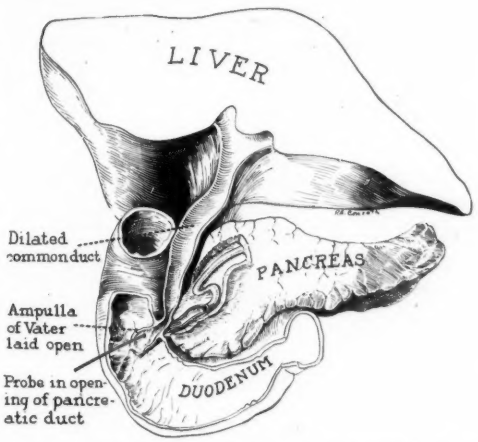


Fig. 1. A drawing of autopsy specimen in Case 1. Note the narrowing of the dilated common duct at its lower end as it passes through the head of the pancreas. The termination of the pancreatic duct is well within the common duct inside the sphincter of Oddi (ampulla of Vater). The same arrangement was found in the other autopsied case (Case 6).

Case 1. L. M., 58 year old housewife entered Barnes Hospital (No. 23163) first on January 1, 1930, complaining of severe attacks of epigastric pain going through to her back and around the costal margin to the right shoulder, lasting several hours, and not relieved by medication. A barium meal and gastro-intestinal X-ray series were negative; but a cholecystogram showed no shadow. On admission she was still suffering from an attack of the previous day and on examination showed tenderness and muscle spasm and guard in both upper quadrants, especially on the right. The other examinations were negative; temperature and pulse were normal. At operation the

TABLE I.—SUMMARY OF CASES OF PANCREATIC INFLAMMATION

Case	Age Sex	Location of pain	Tenderness	Jaundice	Pancreatic lesion	Gall bladder	Stones	Blood amylase	Outcome
1	58 F	Epigastrium, right and left hypochondrium	Over pancreas (X-ray)	+	Fat necrosis A.I.P.*	Cholesterolosis	0	?	Recurrent pain after cholecystectomy: secondary operation, death
2	57 F	Epigastrium, left sided once	Epigastrium and to left	0	Fat necrosis A.I.P.	Chronic inflammation	+	?	Cholecystectomy: cysticocholedochostomy: cured
3	38 F	Epigastrium, left and right radiation	Left hypochondrium	+	?	Chronic inflammation	+	+	Recurrent pain after cholecystectomy
4	30 F	Epigastrium, distention	Epigastrium	+	Fat necrosis	Chronic inflammation	+	+	Cholecystectomy. Cysticocholedochostomy: cured
5	34 F	Left hypochondrium, distention	Epigastrium and left hypochondrium	?	Hard induration and edema	?	?	?	Recurrent pain after cholecystectomy. Secondary operation. Subsidence of attacks
6	54 M	Around umbilicus	Diffuse	+	A.I.P. abscess	Chronic inflammation	0	?	Death after cholecystectomy

*A.I.P.=acute interstitial pancreatitis as shown by microscopic section

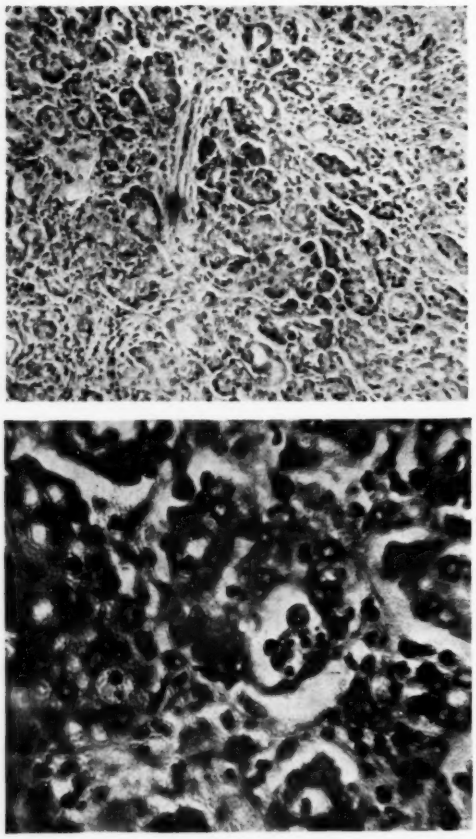


Fig. 2. Photomicrograph of the pancreas in Case 1. The upper view is the low power and represents extensive infiltration with polymorphonuclear leucocytes, some edema but no hemorrhage. The acinar cells are intact. Evidence of old fibrosis is also seen, indicative of previous attacks of inflammation. The lower view represents a higher magnification. Note the presence of leucocytes within a duct as well as between acini.

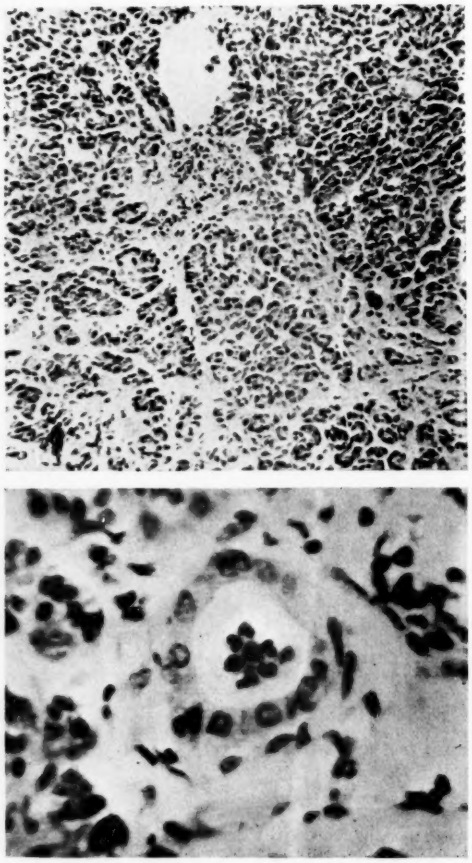


Fig. 3. Photomicrograph of biopsy specimen of pancreas in Case 2. The upper view is a lower power magnification and shows extensive infiltration with polymorphonuclear leucocytes, some edema, but no hemorrhage or necrosis. Slight fibrosis was present indicative of previous inflammation. The lower view shows, under higher magnification, several polymorphonuclear leucocytes within the lumen of a duct with definite surrounding edema.

next day the appendix and gall bladder were removed. No note was made as to the pancreas by the operator. Recovery was uneventful. The gall bladder on examination showed cholesterolosis (strawberry gall bladder), contained no stones, and on section showed some evidence of chronic inflammation. The patient's second admission was on November 6, 1933, about 3½ years later. At this time she stated that the painful attacks were not relieved by her operation but began to recur 3 months after she left the hospital. They were not very severe until 2 months ago when she was awakened at 3:00 a.m. with pain which radiated between the shoulder blades, and she vomited clear fluid. This attack subsided but two other attacks occurred, the last one the day before admission. Jaundice was observed and there was a loss of 27 pounds in weight. Examination disclosed a moderate icterus (urine bile stained, icteric index 31, van den Bergh reaction—immediate direct and positive indirect); white blood cells, 8,350; pulse and temperature, normal. There was a postoperative hernia through which marked tenderness was elicited. On deep pressure through this defect, the pain was excruciating. Under the fluoroscope after a barium meal, the duodenal curve was widened, indicative of pancreatic disease, suggestive of carcinoma, although the extreme tenderness which was localized over this area prevented palpation of a mass.

At operation 1 week after admission, the common duct was opened, but no stone was found. The pancreas was enlarged and firm. During the exploration, the patient's circulation began to fail and in spite of all medication

exodus occurred. At autopsy the pancreas was sectioned and found to be the site of extensive acute inflammation besides much old fibrosis. Numerous areas of fat necrosis were seen in the capsule. The cells of the pancreas itself, however, were intact (Fig. 2). No carcinoma was present. The common duct was slit open and found to be dilated but contained no stones and was narrowed for several centimeters as it passed through the head of the swollen pancreas. In its lumen about 3 or 4 millimeters above the sphincter was the opening of the main pancreatic duct (Fig. 1). Section of the common duct and duodenum showed no acute lesion. The liver was normal grossly and microscopically except for occasional nests of round cells in the periportal areas.

CASE 2. M.G., 57 year old housewife, entered St. Louis City Hospital (No. 12512) October 27, 1933, with the complaint of intermittent attacks of epigastric pain with freedom during the intervals. The present attack began 10 days previously. On admission to the hospital, pulse, temperature, and leucocyte count were normal, there was extreme tenderness in the right and left epigastrium, most marked on the left. She vomited repeatedly and gastric analysis after a test meal revealed no acidity. Cholecystogram showed no shadow; gastro-intestinal series after barium meal was negative. The attack subsided but on the fourth day recurred and a note was made by the senior interne that the "pain was on the left side just above the umbilicus and extending around to the left." Two weeks after admission and 2 days before operation I saw her in another attack and on cursory examination found tenderness in the mid-epigastrium and over the gall-bladder area. Operation on November 11, 1933, revealed a gall bladder with many small stones, and an enlarged indurated pancreas. After cholecystectomy, the cystic duct was found patent and I explored the common duct, of normal size, through it. A small stone similar to those in the gall bladder was fished out of the lower common duct. A bulb tipped probe was passed to the duodenum readily but it encountered a definite resistance at the ampulla. I sewed a catheter into the cystic duct. The pancreas was then exposed through the gastrocolic omentum and the organ inspected over most of its length. Numerous white areas of fat necrosis were distributed over the capsule of the gland and the immediate fat surrounding it. The parenchyma was of a much paler pink color than normal, and the entire gland was indurated and hard especially at the head. I removed a portion of the pancreas for biopsy (Fig. 3) from the body of the gland and closed the defect with sutures; there was slight bleeding and only momentary escape of pancreatic juice.

Drainage of bile continued for 11 days when the tube came out, and then drainage ceased. Recovery was uneventful. Patient has been free of symptoms since then (1 year).

CASE 3. L.B., housewife, age 38, entered St. Louis City Hospital (No. 13657) for the first time on October 6, 1933, with onset 3 days before consisting of pain in the left side, radiating to the right side and then over the entire abdomen; she vomited repeatedly. Opiates relieved the pain hardly at all. On admission to the hospital she was tender only over the right upper quadrant; pulse, temperature, and leucocyte count were normal. Cholecystogram showed no shadow. A diagnosis of cholecystitis was made. At operation (October 24, 1933), the gall bladder was found to contain a few stones. Cholecystectomy was followed by an uneventful recovery. No note was made by the operator as to condition of the pancreas or common duct.

She was admitted again on November 16, 1933, a week after discharge, with recurrence of the same pain that she had had before operation. She pointed to the left of the midline and had pain also in the small of the back. The attack was about over when she was admitted to the hospital and she was discharged 3 days later. The scleræ were questionally icteric.

Her third admission was 1 week later, 12 hours after the onset of another severe attack. The pain and tenderness were localized to the left hypochondrium and radiated to the back, but later was felt also on the right side and right shoulder. I saw her the next day and she was in obvious distress and was vomiting repeatedly. The white count was normal. The pancreatic area could be easily felt through a wide diastasis of the rectus muscles and was definitely tender both to the left and right of the midline. Although her scleræ were not icteric, blood serum examined at this time was distinctly yellow, though its bilirubin content unfortunately was not measured. The blood amylase at this time (24 hours after onset of the attack) was 75 units (normal is 5, according to technique previously described) (5). Two days later a second specimen contained but 20 units. Although the plasma was less yellow in color its icteric index was 13; the van den Bergh showed a delayed direct and positive indirect reaction. By December 4 (6 days after admission), the blood amylase was normal (5 units), and the serum of normal color.

During this time the symptoms gradually and completely disappeared. The temperature dropped from 38.5 degrees C. (101.4 degrees F.) to normal and the pulse from a rate as high as 148 to normal. On discharge she was urged to eat frequently to maintain a steady flow of bile and aid in keeping the biliary tract open. She has had no recurrence of pain (6 months).

CASE 4. A.S., a housewife, age 39 years, was admitted to St. Louis City Hospital (No. 8597) with a history of recurrent epigastric pain for the past 3 years accompanied by vomiting and jaundice. The present attack, the most severe of all, began 2 days ago. The pain did not radiate. Examination revealed an obese woman in severe pain, vomiting repeatedly, with a tense distended abdomen, tender however only in the mid-epigastrium. The scleræ were slightly yellow. Temperature was 37 degrees C. (98.4 degrees F.); pulse, 70; respiration, 20, white blood count, 18,000. Blood amylase was ten times the normal value. Icteric index was 12; van den Bergh, slightly positive; direct, delayed. Under conservative care, pain and vomiting gradually subsided and with it the blood amylase returned almost to normal 4 days later. Cholecystogram revealed no shadow. At operation a chronically inflamed gall bladder containing several stones was removed and the common duct explored through the open cystic duct which was then drained by sewing a catheter into it. The pancreas felt hard and enlarged. When it was exposed through the gastrocolic omentum numerous pinpoint areas of fat necrosis were seen; biopsy was done; section showed the acuteness of the lesion, whereas the gall bladder revealed only chronic inflammation. The postoperative course was uneventful; the cysticocholedochostomy tube drained bile for a week, came out, and the wound closed spontaneously. Patient has remained free from symptoms.

CASE 5. Female,[1] age 34 years, entered the hospital on January 20, 1932, complaining of sudden and extremely severe pain in the upper left abdomen which came on the day before, after eating a hearty evening meal. The pain radiated around to the back and the left of the chest. Morphia gave no relief. Vomiting was frequent. She had had previously two similar, severe attacks, and many less severe and of shorter duration. The patient had been operated on about 8 years ago for appendicitis and cholecy-

[1]Details of this case were kindly furnished by Dr. Raymond L. Zech, Seattle, Washington.

stitis, at which time the gall bladder was drained. Six years later (2 years ago) it was removed. No information was available as to the condition of the pancreas.

Examination revealed marked tenderness in the epigastrium and left hypochondrium. Rigidity was confined to the left upper abdomen and epigastrium. The temperature was 37 degrees C. (99 degrees F.); pulse, plus 80. In spite of the extreme pain and tenderness, she did not appear shocked. On January 20, 1932, a blood count showed hemoglobin of 74, erythrocytes 3,900,000 and leucocytes 9,500; polymorphonuclears, 65 and mononuclears 35. Calcium chloride was given intravenously (15 grains) with no relief of pain. Morphia (½ grain) gave only slight relief. The next day the leucocyte count was increased to 14,500; polymorphonuclears 83 and mononuclears 17. Pain was still severe and the patient started to hiccough, but this did not continue long. The following day the leucocyte count was but 7,950 with polymorphonuclears 56 and mononuclears 44. Blood chemistry analysis showed: blood chloride, 445.5 grams; blood sugar, 72 milligrams. Diastatic index (Meyer and Killian technique) was 16 milligrams (normal). Plain X-ray plate of the abdomen was negative. From the history of repeated attacks, the characteristic pain associated with vomiting which was not fecal in nature, the tenderness confined to the region of the pancreas, the characteristic and localized rigidity and the history of the previous operations, a diagnosis of acute pancreatic necrosis was made, and an operation was advised. The patient, however, refused further surgery. On January 23, she started to improve and was discharged on January 27, 1932 (1 week after admission) following which she had one or two short attacks of pain in spite of a diet almost entirely free from fats. On her next admission, August 8, 1932, during another attack, considerable abdominal distention was present. The tenderness and rigidity were most marked over the left upper quadrant. At operation no intestinal obstruction was noted; the bile ducts were negative. The duodenum was adherent to the liver. Through an opening in the gastrocolic omentum, the pancreas was exposed and found to be enlarged and thickened throughout and edematous in appearance. Recovery was uneventful and the patient after discharge reported that attacks recur every 3 or 4 months but are not so severe, though they do confine her to bed for a few days each time.

Case 6. W.R., a salesman, age 54 years, was admitted to St. Louis City Hospital (No. 16974) January 10, 1934. Six months before he had an attack of indigestion which subsided, to recur in 2 months, this time with pain around the umbilicus and jaundice which became severe and was accompanied by clay colored stools; it subsided in 2 weeks. The patient did not stop his work. Jaundice recurred 2 days before admission, and he had a chill, fever, and pain around his umbilicus which did not radiate. Examination revealed the patient ill and markedly jaundiced (icteric index 63) with the abdomen slightly distended, but tender and resistant everywhere especially in the right upper quadrant. Pulse rate was 76; temperature, 37 degrees C. (98 degrees F.), although it did reach 38.5 degrees C. (101 degrees F.) on one occasion. The leucocyte count was 17,000; bleeding time ½ minute and clotting time 3½ minutes. My impression was acute cholecystitis with stone in the common duct. The acute process subsided rapidly and his jaundice, pain, and rigidity cleared up completely within a week. At operation January 21, 1933, I found a shrunken gall bladder containing no stones. The common duct was dilated; after cholecystectomy I explored it through the patent cystic duct, but no stones were found. A bulbed probe entered the duodenum but only after passing a definite resistance at the ampulla. The liver was small and cirrhotic, the spleen was soft and three times its normal size. The pancreas felt enlarged and indurated. An attempt to expose the gland through the gastrocolic omentum was given up because of the extensive adhesions joining the two structures and because marked bleeding was encountered. I sewed a catheter into the cystic duct for drainage. The bile was clear and amber in color and drained profusely during and after operation. A transfusion of 500 cubic centimeters of blood had been prepared ahead of time and was given at the conclusion of the operation although his general condition was good. It remained so for 36 hours when he suddenly became cyanotic, weak, heart sounds distant, developed râles in his chest, and expired 6 hours afterward. At autopsy there was found a pulmonary edema and extensive arterial disease of the aorta. A fine probe passed in the common duct by the pathologist was found to enter the pancreas directly, due, as was found after dissection, to the fact that the pancreatic duct opened into the common duct several millimeters above the sphincter, which was tight and contracted. No stones were found anywhere. The pancreas was large, firm, and adherent everywhere. The cut section showed a small abscess in the head near the dorsal surface and surrounded by several smaller abscesses. No hemorrhage, gangrene, or softening in the parenchyma itself were found. There was no fat necrosis. Sections of the gland showed an acute picture similar to that of Cases 1 and 2. There was no duodenitis and the common duct showed only an old fibrotic infiltration, with no leucocytic cells. The liver showed chronic fibrotic changes. The tissue unfortunately was allowed to develop postmortem changes which made the microscopic sections unsuitable for obtaining adequate photomicrographs.

Deductions

Six cases of acute inflammation of the pancreas are described, the diagnosis being based in 5 by anatomical proof (2 at autopsy, 2 by biopsy, and 1 by direct inspection at operation) and in the other by the recurrence of rather characteristic pain after previous cholecystectomy (during which there was an increased blood amylase). All were patients with proved gall-bladder disease; 3 had had a cholecystectomy but returned with recurrent pain, the 3 others were operated on for gall-bladder disease, 2 with and the other without stones. Clinically the location of the pain and tenderness in the mid and left epigastrium over the pancreatic area in 4 cases suggested rather definitely inflammation of this gland. The blood in 2 patients was found to contain a high amylase content.

The importance of pancreatic involvement in gall-bladder disease has generally been denied, for it has been assumed that the lesion is silent and that it has only theoretical interest. The fact, however, that such a lesion may be responsible for recurrent pain after cholecystectomy gives it definite practical importance. The observations recorded herein point to such an association and when taken with data previously recorded (4) emphasize the dominant part that the pancreas

may play in the production of epigastric pain, not only when disease of the gall bladder is also present or has been removed but also in cases in which it contains the only abdominal lesion. The evidence also indicates that pancreatitis is far from silent and that the symptoms it causes are frequently characteristic and often easily distinguished from those produced by gall-bladder disease alone. The fact, finally, that knowledge of the pathogenesis of this type of pancreatic inflammation is still incomplete should stimulate further study in order that adequate measures for the prevention and treatment of the lesion might be instituted.

The term "acute interstitial pancreatitis" will be used in describing the lesion in the present cases since the microscopic sections in 3 of them (Cases 1, 2, and 6, Figs. 2 and 3) showed the same inflammatory signs noted in those previously reported (4). These signs, briefly, consist of marked infiltration of acute polymorphonuclear cells into the interlobular as well as interacinar tissue. In addition such cells are frequently found within the lumen of the finer ducts suggesting a duct borne infection. At any rate the presence of these cells indicates an acute process, which is borne out by the occurrence of edema in many places. The presence of fat necrosis in 3 cases also points to the acute nature of the lesion. Nevertheless, one sees no evidence of the cell necrosis or hemorrhage characteristic of acute hemorrhagic pancreatitis even though in some cases the duration of the disease was long enough to have produced it. In addition to acute signs there was evidence of previous subsided inflammation in the frequent interlobular and interacinar fibrosis. In only 1 of these cases was there suppuration (Case 6) present.

The reasons for using the designation "acute interstitial pancreatitis," as distinguished from "acute pancreatic necrosis," were discussed in my previous paper (4). It is obviously impossible to say that we are dealing with two different diseases until the pathogenesis is better known. It may be that they represent the same disease in a severe and mild form. The striking difference in the clinical picture of acute pancreatic necrosis and the cases here presented seems sufficient to warrant separate consideration. Moreover, the apparent frequency of the present type of pancreatitis and its tendency to be overlooked in biliary disease would seem to justify, for the time being at least, considering it as a separate clinical entity.

Further comment on the present observations will be made as follows:

PATHOGENESIS

Of the many theories of the genesis of pancreatic inflammation that of regurgitation of bile into the pancreatic duct from the common duct has aroused the most interest. Such an event is made possible by the presence of an impacted stone in the ampulla. Unfortunately for this theory, a stone is not always present in these cases. Moreover, it has been shown by Mann and Giordano that the anatomical arrangement necessary for such an event is too infrequent to be of practical importance. The suggestion of Archibald that this reflux could occur even in absence of stone, by a spasm of the Oddi's sphincter, made the idea more plausible for the anatomical arrangement of the ducts is such in 20 per cent of humans that the common sphincter by spasm could conceivably convert the biliary and pancreatic ducts into a continuous channel. This could be achieved by even a tiny impacted stone in but 4 per cent of cases (Mann and Giordano).

This idea is supported by the autopsy findings on Case 1, for the pancreatic duct emptied into the common duct several millimeters proximal to the sphincter of Oddi so that bile could easily flow into the pancreas if the papilla were closed for any length of time. The microscopic section of the pancreas too showed acute inflammatory cells within the ducts (Fig. 2). The same anatomical arrangement was noted at autopsy in Case 6; indeed, the pathologist who probed the common duct noted that it went directly into the pancreatic duct and not into the duodenum at all. It is of interest too that in Case 2, evidence of sphincter spasm was noted at operation by the temporary impediment offered a bulbed probe which was passed through it into the duodenum, and that the lumen of the pancreatic duct in the biopsy specimen also contained inflammatory cells (Fig. 3).

Additional observations of a direct communication between the pancreatic and common ducts in cases of pancreatic disease is furnished by Nordmann who states that in 2 cases in which the gall bladder was drained pancreatic juice was demonstrated in the fluid draining from the cholecystostomy wound. Other examples have been mentioned before (4). The observations of Popper add further evidence of its importance. He found pancreatic ferments in the gall-bladder bile in 16 of 18 cases of pancreatitis. In a case described by R. M. Jones clear pancreatic juice flowed from a drainage tract placed at a local area of pancreatic necrosis. A communication with the biliary tract was shown by the presence of bile in the discharge after removal of the gall-bladder drain (10).

The origin of pancreatitis from adjacent disease is another possibility. That the duodenum is its site is not supported by the autopsy findings in Cases 1 and 6. In Case 5, on the other hand, an adherent duodenum was found at operation, which may, however, have been due to the two previous operations. The liver and common duct are other possible sources, but with the exception of the cirrhosis in Case 6 the evidence thus far is against it. The fact that this type of pancreatitis may occur without gall-bladder disease and after its removal would seem to exclude the gall bladder as its source especially in view of the conflicting evidence as regards the lymphatic connection between the pancreas and gall bladder (6).

CLINICAL MANIFESTATIONS

Pain was present in all cases and in 3 was quite severe. In Case 1, fluoroscopy revealed the fact that the pancreas was the site of tenderness by localizing it inside the duodenal curve (visualized by the barium meal). This was aided by a large hernial defect in the old operative scar which made deep palpation possible. It is interesting nevertheless that the pain was felt on the right side. In Case 2 the picture was so characteristic of ordinary biliary colic in one attack that I did not even suspect pancreatic involvement although during another attack left sided localization was definitely noted by another observer. In this case, although the presence of stones in the gall bladder and common duct pointed to biliary colic as the cause of the painful attacks, the fat necrosis around the pancreas and the acute inflammatory signs shown on section of the biopsy specimen indicated that it may well have been the cause of the acute symptoms which were present before operation. A definite left sided location of the pain was present in Cases 2, 3, and 5. Tenderness, moreover, coincided with the transverse position of the pancreas. Zones of hyperesthesia were not tested for and perhaps should be more often elicited. In Case 6, the only pain experienced was around the umbilicus, although tenderness was in the upper right quadrant.

In the paper already referred to (4) on acute interstitial pancreatitis the location and nature of the pain was more fully discussed. While in certain instances the left sided localization suggests its origin from the pancreas, pain referred to the back was also frequent and present also in the cases presented above. The fact that the pain is on the right side, however, does not rule out the pancreas. Several such instances were described in my previous paper. Case 1, herein, is another, for here the gall bladder had been removed—yet the pain was right sided and only under the fluoroscope was it clear that the tenderness coincided with the tissue inside the duodenal curve. The tendency of the pain to subside, sometimes within a few hours, corroborates the findings of Guleke mentioned above. Abdominal distention was present in Cases 4 and 5, of a degree suggesting intestinal obstruction, a diagnosis which was made in many of the cases previously reported (4).

The prognosis of this type of pancreatitis especially as far as the attacks of pain are concerned seems good. In Case 5 the frequency and severity gradually diminished. In another case (No. 35) of recurrent pain after cholecystectomy described in a previous paper (4) the patient had a definitely acute pancreatic lesion as shown by biopsy; the attacks, after operation, though at first severe and requiring morphia, gradually abated over a course of 3 years and then entirely disappeared, never to return. The tendency of this type of pancreatitis to develop into acute necrosis is apparently remote.

BLOOD AMYLASE

The blood amylase as measured in Cases 3 and 4 was very high and became lower with the subsidence of the attack.[1] In Case 5, the value was presumably normal, but the blood was examined 3 days after the onset of the attack and by a method which is open to criticism (5).

LEUCOCYTOSIS

Leucocytosis of moderate degree was present in most cases. In Case 5 it reflected rather well the severity of the symptoms. In Cases 1 and 3, however, the white cell count was normal.

JAUNDICE

Jaundice was present in at least 4 of the present cases (1, 3, 4, and 6). It is of interest that in 2 of them no stones were ever found and in another stones in the gall bladder had been removed previously. The mechanism of jaundice was probably not intrahepatic; of the 4 jaundiced cases, in Case 1, there was no anatomical evidence of hepatitis at autopsy; in Case 3 no special tenderness over the liver was made out clinically although a liver function test unfortunately was not done; in Case 6 although the liver was the site of a cirrhosis it was of the atrophic type which is not apt to produce jaundice.

That the jaundice was extrahepatic from pressure on the lower end of the common duct as it traverses the head of the pancreas, swollen by the

[1] Exactly the same observations were made in another case. The patient was operated on by another surgeon who found a gall bladder with stones which was removed; the pancreas was not inspected.

acute inflammation, seems clear from the autopsy findings in Case 1. This patient had clinical jaundice just before death and the dilated common duct narrowed markedly as it passed through the swollen pancreatic parenchyma for a distance of several centimeters. This is shown in the accompanying drawing (Fig. 1) but was even more definite at the time of autopsy. The same was true of Case 6. In this patient the jaundice had been intense although it had subsided a week before his death.

The anatomical conditions for such a compression of the lower common duct are present in a large percentage of individuals. Thus in 40 dissections, Ruge found that in 32 (80 per cent), and in 58 cases v. Bungner found that in 55 (95 per cent) the lower end of the common duct was completely surrounded by pancreatic parenchyma and that in all cases it is in contact with the head of the gland for a considerable distance. In a previous communication (5) from this clinic, a case (No. 32) was cited in which a total biliary obstruction supposed clinically to be due to a carcinoma of the head of the pancreas actually was due to contraction of fibrous tissue in an indurated pancreas around the lower common duct. In another paper (4) attention was called to the frequency with which a dilated tense gall bladder was found in cases of edematous (acute interstitial) pancreatitis even when the biliary tract itself appeared free of infection. These observations all suggest that stone or hepatitis is perhaps only rarely the cause of the jaundice in these cases, and that a mechanical obstruction due to edema, or fibrous contraction about the common duct as it passes through the head of the pancreas (or perhaps sphincter spasm at the papilla of Vater itself) may frequently play the most important rôle. It would seem that the liver function test of Graham and Cole would be of diagnostic value, for it is normal in cases of jaundice due to such a mechanical cause, in contrast to a high retention in stone and hepatitis.

It is interesting to emphasize again (4) the fact that fat necrosis about the pancreas may be present in this type of pancreatic inflammation (Cases 1, 2, and 4). It is not, as is often stated, pathognomonic of acute hemorrhagic pancreatitis, although frequently, but not always, noted in this lesion.

TREATMENT

If we assume from the evidence already presented that interstitial pancreatitis produces symptoms, treatment becomes important. And if the recurrent pain after cholecystectomy is often due to such a lesion the necessity for new or additional therapy becomes more urgent. It is difficult, of course, to recommend any special treatment until pathogenesis is more completely known. If regurgitation of bile into the pancreatic duct plays the decisive rôle, drainage of bile at least temporarily, would seem to be indicated. This has long been recognized as an important procedure in cases of pancreatic necrosis. But where only an indurated pancreas is found, biliary drainage has found few, although enthusiastic, proponents. Most surgeons content themselves with cholecystectomy and do nothing about the pancreatic lesion.

On theoretical grounds, cholecystectomy alone should minimize regurgitation of bile by bringing about an insufficiency of the Oddi sphincter, since bile must now flow continuously in absence of the storage function of the gall bladder. At least it has been shown experimentally that removal of the gall bladder is followed by dilatation of the common duct and relaxation of the sphincter. Clinically this has also been shown to occur. Practically, however, it must be admitted that when the gall-bladder function is gone at the time of operation, and the common duct is dilated already, it is difficult to see how removal of the diseased and often obstructed gall bladder will change the size or function of opening at the lower end of the common duct. The actual recurrence of symptoms after cholecystectomy, in the cases mentioned at least, constitutes an added argument against the supposition that cholecystectomy alone is sufficient. On the other hand the spontaneous, though occasionally slow, subsidence of symptoms in several of the cases which have been mentioned suggests that some such readjustment as this may occur and explain the relief of symptoms.

The idea that removal of the gall bladder as a focus of infection henceforth prevents transmission of infection to the pancreas likewise is not supported by the cases of pancreatitis noted after cholecystectomy (Cases 1, 3, and 5). Infection, of course, may not be confined to the gall bladder. The liver or the wall of the common duct may harbor organisms which are lighted up from time to time and produce symptoms, or a duodenitis may be the starting point. These sites of infection, however, were not demonstrable in any of the cases here reported even in the 2 examined at autopsy. On the other hand, we are not sure that in the case of pancreatitis the infection does not actually start in the pancreas. Thus, in a previous paper (4), many instances were cited in which disease of the gall bladder was absent, the pancreatitis being the only demonstrable lesion.

To drain bile for a short period of time, or at least provide a by-pass for its escape is a rational procedure if we assume that bile may otherwise be able to enter the pancreas and continue the inflammatory process. Whether a short period of drainage has any permanent effect cannot at present be definitely stated. Diversion of bile by choledochostomy has the disadvantage that it adds to the mortality of the operation and in a few cases may lead to subsequent stricture. In Cases 2, 4, and 6, I established biliary drainage without opening the common duct by inserting a catheter into the cystic duct. This procedure, cysticocholedochostomy, was used by Halsted in 1899 and others, according to Reid, who described the procedure in 1921. It was used by Reid to provide drainage after an incision in the common duct had been sutured. It was also described in 1925, by Lobingier. In itself it is a simple enough procedure unless, of course, the cystic duct is definitely occluded. Often, however, the duct is large enough to permit exploration of the common duct and sometimes the hepatic ducts, differences being dependent, of course, on the manner in which it joins the biliary tract. In most cases, however, if patent, it allows probing of the distal part of the common duct, the papilla, and the duodenum quite easily. Bile drainage through a cysticocholedochostomy ordinarily does not last long, often only a week or two, after which the tube comes out and the sinus heals, unless, of course, an obstruction is present. Prolonged bile drainage (for months) has been advocated by some surgeons, but can be achieved only by the insertion of a T tube in the common duct.

Another suggestion, that of actual dilatation of the sphincter of Oddi, merits some consideration and can, of course, be done by means of common duct probes armed with bulbs of increasing caliber. Further observations may show that this procedure is worthy of more extensive use. It can be readily done through the cystic duct, thus avoiding the necessity of opening the common duct, at least in most cases.

One may advise frequent feeding with the idea that otherwise intermittent stasis of bile is functional and may be disadvantageous in these cases. The fact that in several cases attacks came on after a heavy meal also should caution the patient in favor of small frequent feedings. By eating often, a more uninterrupted stimulus to both biliary and pancreatic secretion is effected, which may aid in keeping the channels open and perhaps eventually lead to a dilated sphincter.

There is apparently no necessity for an emergency operation in this type of pancreatitis since the possibility of its developing into acute hemorrhagic pancreatitis, from the evidence thus far available, appears remote. We are dealing, it would seem, with either an entirely different disease and one, moreover, which can often be readily differentiated from pancreatic necrosis, or a mild type which does not go on to hemorrhage and necrosis. The indications for secondary operation in cases with recurrence after cholecystectomy are more difficult to evaluate. If further study shows a sufficiently frequent tendency to spontaneous subsidence of attacks obviously symptomatic treatment is all that is needed. If disability is great and intervention is decided upon, the procedure to be carried out is a difficult problem. Further knowledge of pathogenesis, whether it confirms the assumptions made herein or not, is of course needed. Continued bile drainage with a T tube has been recommended by some, but it has obvious disadvantages. Dilatation of the sphincter might be tried through an opening in the common duct. It is suggested, finally, that, in some cases, especially those with attacks of jaundice, the portion of the pancreas surrounding the lower common duct be resected so as to prevent the biliary occlusion caused by swelling of the pancreas. Another possibility too is actually short-circuiting the bile away from the pancreas by implanting the common duct into the stomach or duodenum at a new site.

SUMMARY

Six cases with acute interstitial pancreatitis are presented as examples of the pancreatic origin of pain and jaundice in patients with gall-bladder disease (3 cases) and in patients with recurrent symptoms after cholecystectomy (3 cases). Evidence is presented that this lesion is an entity which produces a clinical picture which is characteristic and which is distinguishable from frank pancreatic necrosis. The value of blood amylase determinations in its diagnosis is shown. That it has a definite pathogenesis, which depends on an anatomical arrangement by which, during spasm of the sphincter of Oddi, bile may enter the pancreatic duct is indicated by additional evidence. The therapeutic indications which this lesion invites, aside from treatment of the associated biliary disease, are discussed.

BIBLIOGRAPHY

1. Archibald, E. Ann. Surg., 1929, 90: 803.
2. Bungner, O. v. Beitr. z. klin. Chir., 1903, 39: 131.
3. Douglas, J. Ann. Surg., 1933, 98: 909.
4. Elman, R. Surg., Gynec. & Obst., 1933, 57: 291.
5. Elman, R., Arneson, N., and Graham, E. A. Arch Surg., 1921, 19: 943.

6. GRAHAM, E. A. Surgical Diagnosis. Vol. 3, p. 411, Philadelphia: W. B. Saunders & Co., 1930.
7. GRAHAM, E. A., COLE, W. H., COPHER, G. H., and MOORE, S. Diseases of the Gallbladder and Bile Ducts. Philadelphia: Lea and Febiger, 1928.
8. GULEKE, N. Verhandl. d. deutsch. Gesellsch. f. Chir., 1912, 41: 310 (Part 11).
9. JONES, D. F. New England J. Med., 1928, 199: 716.
10. JONES, R. M. Brit. J. Surg., 1934, 22: 296.
11. JUDD, E. S. J. Am. M. Ass., 1921, 77: 197.
12. KEHR, H. Chirurgie der Gallenwege, p. 759. Stuttgart, 1913.
Idem. Praxis der Gallenwege Chirurgie. Vol. 2, p. 324. Munich. 1913.
13. LOBINGIER, A. S. J. Am. M. Ass., 1925, 85: 85.
14. MANN, F. C., and GIORDANO, A. S. Arch. Surg., 1923, 6: 1.
15. MAYO-ROBSON, A. W. Lancet, 1900, 2: 235.
16. MAYO-ROBSON, A. W., and CAMMIDGE, P. J. The Pancreas, Its Surgery and Pathology. Chap. 16, p. 468. Philadelphia: W. B., Saunders Co., 1907.
17. NICOLL, J. H. Brit. M. J., 1919 2: 625.
18. NORDMANN. Verhandl. d. ges. f. Chir., 1913, Part II, p. 362.
19. OPIE, E. L. Diseases of the Pancreas, 2d ed., p. 208. Philadelphia, 1914.
20. POPPER, H. L. Arch. f. klin. Chir., 1933, 175: 660.
21. REID, M. R. Ann. Surg., 1921, 73: 458.
22. RUGE, E. Arch. f. klin. Chir., 1908, 87: 47.
23. TALMAN, I. M. Arch. f. klin. Chir., 1933, 175: 472.

THE TREATMENT OF SENILE VAGINITIS WITH OVARIAN FOLLICULAR HORMONE

M. EDWARD DAVIS, M.D., F.A.C.S., CHICAGO, ILLINOIS

From the Department of Obstetrics and Gynecology, The University of Chicago, and the Chicago Lying-in Hospital

THE term "senile or adhesive vaginitis" describes a non-specific inflammatory condition often occurring during post-menopausal life. Its occurrence is not uncommon in young women in whom an artificial menopause has been produced by surgical or radiation castration. Since this condition is not limited to elderly women, but may also follow the cessation of ovarian function in young women, "post-menopausal vaginitis" would be a more suitable term.

PHYSIOLOGICAL ATROPHIC CHANGES

The physiological atrophic changes which occur in the genital organs after an artificial or spontaneous menopause may be considered the normal sequel of the menopause. The general progressive atrophy of the genitalia during this period affects the vagina in that there is a shortening of the vaginal lumen and a constriction of its diameter, particularly at the introitus. The vaginal vaults may disappear completely and the vaginal walls lose their elasticity and distensibility. These gross changes are due to a loss of elastic tissue and muscle cells in the musculature, which are replaced by rigid connective tissue. The mucosa has a smooth and glistening appearance as the result of a loss of the normal rugæ and the atrophic changes in the squamous epithelium. Excessive stretching of the mucosa on vaginal examination or the trauma of intercourse may lead to superficial mucosal abrasions and petechial hemorrhages.

These physiological changes may develop very slowly over a period of years, becoming more marked with advancing age. Occasionally, an abrupt onset of the menopause in a young woman by removal of the ovaries or radiation castration may produce a rapid development of atrophic changes. The physiological changes may cause the production of no local symptoms other than a dyspareunia.

The squamous epithelium on histological examination consists of only five or six layers of cells. The functionalis has disappeared entirely and there is no evidence of cyclical activity. The cells of the basalis are small and the nuclei and granular cytoplasm are dark on staining. The basal layer of cells is less distinct than during active sex life. Little evidence of cellular activity can be seen.

SENILE VAGINITIS

The development of senile vaginitis follows an inflammation superimposed on the physiological atrophic mucosa of the vagina. The exciting factor may be an irritating uterine discharge which macerates the atrophic vaginal epithelium, or a recurring minor trauma which injures the low inactive squamous epithelium. The usual pathogenic organisms in the vagina invade these denuded unprotected areas and start an inflammatory process. The organisms involved are variable and probably of low virulence. The inflammation may cause superficial ulcerations or erosions of the vaginal mucosa. Grossly, they appear as small, punctate, superficial, hemorrhagic areas. The denuded areas become fused together when in apposition if the process is extensive, forming filmy adhesions which finally organize to form firm adhesions or synechiæ. The cervix may be hidden by these adhesions if they are numerous and rarely the continuity of the vaginal lumen may be lost. This adhesive process is the healing stage of the disease. Thus, adhesive vaginitis is a late stage of senile vaginitis. The condition may become entirely quiescent, but complete obliteration of the vaginal vaults and a large portion of the lumen may be an end-result.

SYMPTOMS

The symptoms of vaginitis are vaginal discharge and burning, pelvic pain and discomfort, smarting on urination, and occasionally pruritis of the vulva. The discharge is usually watery in consistency, grayish-white, and occasionally serosanguineous, which may be suspicious of cancer. The discharge is usually scanty in amount but may be profuse at times. Its irritating character may cause an inflammation of the vulva and urethra, extending over the perineum and onto the groins. Exacerbations of the condition may aggravate the symptoms to such an extent as to cause loss of sleep.

DIAGNOSIS

Senile vaginitis is not difficult to diagnose. A subacute or chronic vaginitis developing during

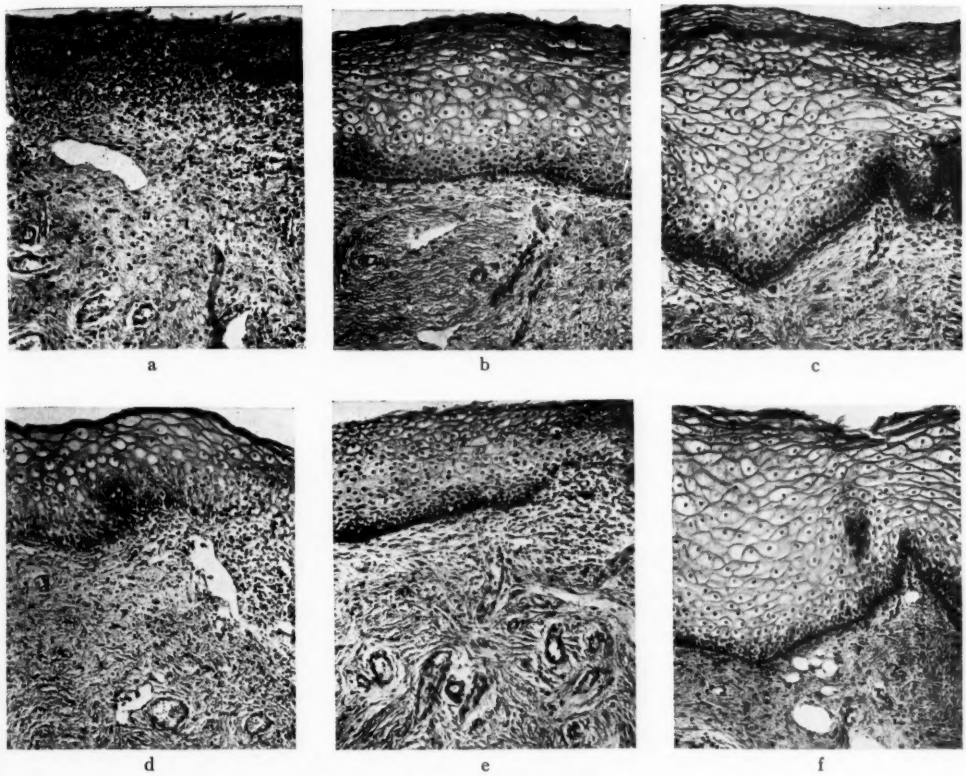


Fig. 1. a, The squamous epithelium consists of four or five layers of cells which are small and indistinct. The basal layer of cells is somewhat irregular. There is no sharp demarcation between the cells and the subepithelial zone. No mitotic figures can be seen. A moderate infiltration of round cells and a few polymorphonuclear leucocytes can be seen in the subepithelial zone, indicative of the inflammatory condition.

b, Note the complete restoration of the squamous epithelium to that seen during active sex life. The basal cells are arranged regularly and show signs of cellular activity. All of the cells are large, clear, sharply demarcated, and contain an abundance of glycogen. The functionalis is beginning to develop. Note the increased vascularity of the subepithelial connective tissue and the compiete disappearance of inflammatory cells.

c, Six weeks after treatment. Note the increasing thickness of the squamous epithelium. The functionalis has been completely restored. The active basal cells comprise several layers.

d, Four weeks after treatment had been discontinued. Note the disappearance of the functionalis and the marked decrease in the thickness of the basalis. These changes demonstrate that regression has occurred on the part of the epithelium.

e, Nine weeks after treatment had been discontinued. Note the continued regression of the squamous epithelium, the complete disappearance of the functionalis, and partial destruction of the basalis. The cells have again decreased in size and all signs of cellular activity in the basal zone have disappeared.

f, The squamous epithelium has been rebuilt to this stage after reinstitution of amniotin treatment for a period of 3 weeks.

(All photomicrographs were magnified 42.5 times for accurate comparison of the squamous epithelium.)

the postmenopausal period is usually of this type. Digital examination frequently reveals the vaginal walls adherent in places by filmy adhesions which may be broken up easily. The vaginal lumen is greatly narrowed and inelastic. Simple examination causes pain and bleeding. Speculum examination reveals a smooth, glistening mucosa with small foci of superficial hemorrhage and loss of epithelium. The introitus may be reddened and irritated, and the inflammation may extend over the perineum and about the anus. The glue-like discharge on microscopic examination consists of epithelial cells, leucocytes, red blood cells, and a host of bacteria. Occasionally, the tri-

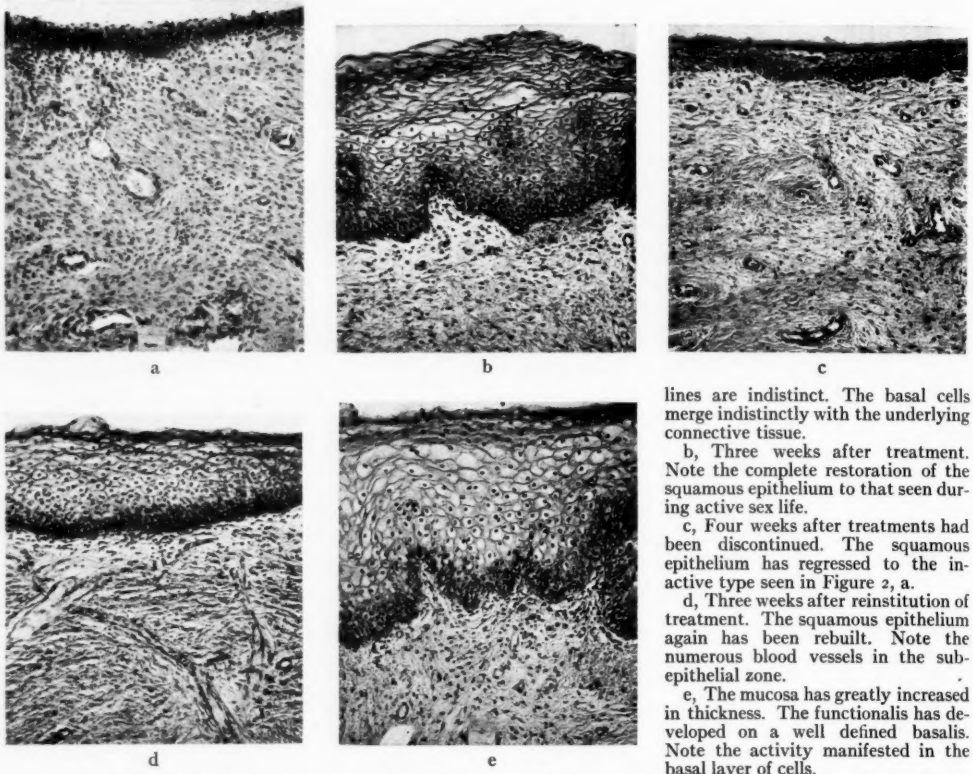


Fig. 2. a, Note the low atrophic squamous epithelium. The cells are small, densely packed together, and their outlines are indistinct. The basal cells merge indistinctly with the underlying connective tissue.

b, Three weeks after treatment. Note the complete restoration of the squamous epithelium to that seen during active sex life.

c, Four weeks after treatments had been discontinued. The squamous epithelium has regressed to the inactive type seen in Figure 2, a.

d, Three weeks after reinstitution of treatment. The squamous epithelium again has been rebuilt. Note the numerous blood vessels in the subepithelial zone.

e, The mucosa has greatly increased in thickness. The functionalis has developed on a well defined basalis. Note the activity manifested in the basal layer of cells.

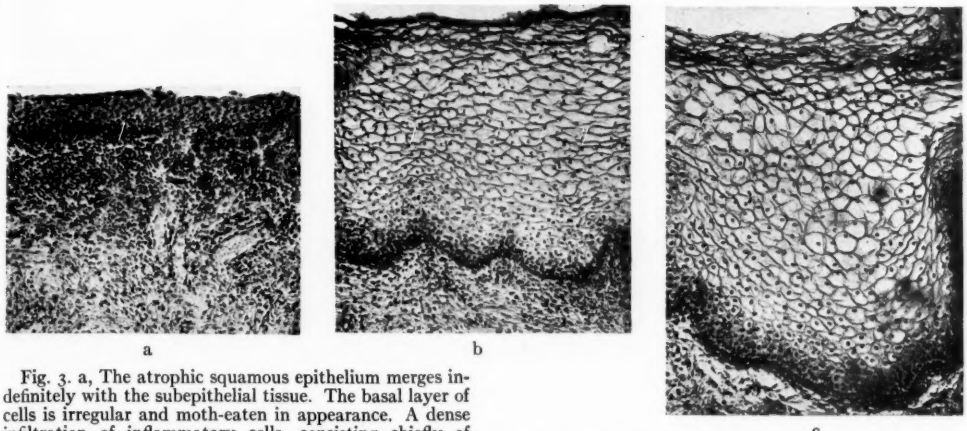
(All photomicrographs were magnified 42.5 times for accurate comparison of the squamous epithelium.)

chomonas parasite is found complicating the varied bacterial flora. It is impossible to state whether this organism is an opportunist, making the most of unusual environmental conditions, or whether it is the primary offender. Gonorrheal vaginitis, rarely occurring during this time, may be ruled out by the Gram-stain method.

PRESENT DATA

The patients in this series all had an artificial or spontaneous menopause. They all complained of the characteristic symptoms of senile vaginitis, which was confirmed on examination. Many of them had been patients in our own clinic for several months and their condition had failed to respond to the usual therapy. Some of them had been treated elsewhere at various times, with little or no improvement. In each instance, a biopsy specimen was taken from the vagina before treatment was instituted, with repeated biopsies every 3 weeks for a period of 4 or 5 months. Biopsies of the vagina can be removed without pain by the injection of a small amount of novocain locally, according to the method described in a previous communication. All other treatment was discontinued. In some instances it was difficult to persuade the patient to refrain from taking vaginal douches containing various medicaments which they had used for years.

The cases were divided into several groups, according to the type of treatment. The largest group received 100 rat units of amniotin (Squibb) subcutaneously three times weekly. In addition to this, a vaginal suppository containing 75 rat units of amniotin was used each night. The duration of the treatment averaged 6 weeks, although in most instances the symptoms disappeared after the first 10 days. A second group of patients received only subcutaneous injections of 100 rat units of amniotin. This was done to eliminate the



a b c

Fig. 3. a, The atrophic squamous epithelium merges indefinitely with the subepithelial tissue. The basal layer of cells is irregular and moth-eaten in appearance. A dense infiltration of inflammatory cells, consisting chiefly of round cells, can be seen lying beneath the squamous epithelium.

b, Three weeks after treatment. The squamous layer has been rebuilt to several times the previous thickness. The basal layer of cells is arranged regularly and shows signs of activity. The large, clear cells of the basalis contain an abundance of glycogen.

c, Under continued treatment an increasing thickness of the squamous epithelium can be seen. The individual cells have increased in size. A well developed functionalis is now apparent. The interepithelial zone of cornification likewise can be noted.

(All photomicrographs were magnified 42.5 times for accurate comparison of the squamous epithelium.)

effect of the inert ingredients of the suppositories as an important factor in the therapy. The last group of women received only suppositories. These patients responded very poorly, so the subcutaneous administration of amniotin was added to the therapy.

The biopsy findings and a short résumé of selected cases are given to illustrate the effect of the treatment.

CASE REPORTS

CASE 1. A. L., Unit No. 6337, aged 73 years, was first seen December 5, 1932, complaining of vaginal irritation, burning on urination, and pelvic discomfort. She was wearing a pessary for relief of anterior and posterior relaxation. On October 31 1933, an anterior and posterior colporrhaphy was performed. However, the symptoms still persisted and the vaginal irritation was so marked that she was referred for amniotin therapy. On vaginal examination the mucosa was found to be thin and atrophic, some raw areas and numerous petechial hemorrhages were present, and multiple filmy adhesions obliterated the fornices. A glue-like, grayish-white irritating discharge was noted.

Material for biopsy examination was taken on August 3, 1934, and 100 rat units of amniotin were given subcutaneously three times weekly (Fig. 1, a). After 3 weeks' time all symptoms disappeared and the vaginal mucosa appeared normal.

Second biopsy taken August 24, 1934 (Fig. 1, b); amniotin continued.

Third biopsy taken September 7, 1934 (Fig. 1, c); amniotin discontinued.

Fourth biopsy taken October 5, 1934 (Fig. 1, d). The patient was still symptom free and the mucosa appeared normal, but distinctly thinner and more glistening than on the previous examination.

On November 9, 1934, the patient stated that the symptoms of vaginal irritation, discharge, and pelvic discomfort returned within the last week or 10 days. She complained of some burning on urination and loss of sleep. Microscopic examination of the discharge showed bacteria of non-specific origin. A fifth biopsy was taken and amniotin therapy resumed (Fig. 1, e).

A sixth biopsy on December 21, 1934, showed that the vaginal mucosa had returned to normal (Fig. 1, f).

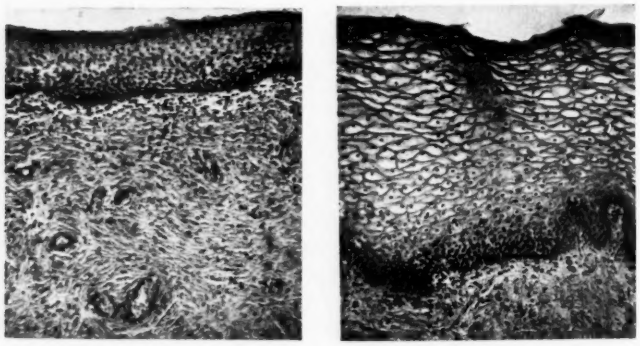
On the patient's last visit to the clinic, January 11, 1935, the vagina appeared entirely normal and she was still symptom free.

CASE 2. M. M., Unit No. 105129, aged 43 years, had a right oophorectomy in 1921 for an ovarian cyst, and a left oophorectomy in 1923 for a similar condition. Amenorrhea followed operation. The symptoms became progressively worse over a period of 5 years, in spite of local therapy. On vaginal examination the mucosa was markedly reddened, the vagina was constricted and had lost most of its normal elasticity. Speculum examination revealed multiple petechial hemorrhages throughout the mucosa, areas of roughening and filmy adhesions obliterating the anterior and posterior vaults of the vagina. Examination provoked profuse bleeding.

Biopsy material was taken on August 10, 1934, and 100 rat units of amniotin were given subcutaneously three times weekly and one vaginal suppository nightly (Fig. 2, a).

Examination on September 7, 1934, showed marked improvement in the patient's condition. The vagina easily admitted the speculum. The mucosa was soft and distensible, and the superficial hemorrhages and filmy adhesions had entirely disappeared. A second biopsy was taken and amniotin therapy discontinued (Fig. 2, b).

The patient returned on October 9, 1934, complaining of a burning sensation in the vagina, burning on urination, dull pelvic pain, and an irritating discharge. She had felt well for about 3 weeks after the treatments were discontinued, but during the last 3 weeks the symptoms returned. A third biopsy was taken and amniotin treatment was instituted (Fig. 2, c).



a b

Fig. 4. a, The squamous epithelium before treatment.
b, Three weeks after treatment. Note the marked increase in the thickness of the squamous epithelium. The basal layer consists of three or four rows of actively growing cells. A dense functionalis is developing.
(All photomicrographs were magnified 42.5 times for accurate comparison of the squamous epithelium.)

Examination on November 23, 1934, revealed a normal appearing mucosa. The patient had no complaints. A fourth biopsy was taken and amniotin treatment continued (Fig. 2, d).

On December 14, 1934, a fifth biopsy was taken. The mucosa appeared normal and the patient's condition was improved. Since this time she has used three or four vaginal suppositories weekly for 6 weeks. The vaginal mucosa has retained its normal healthy condition and she is apparently entirely cured.

CASE 3. Van E., Unit No. 85172, aged 65 years, was first seen on June 29, 1934, complaining of marked burning and discomfort in the vagina and on urination. Local treatment was of no avail and the symptoms became steadily worse. The patient had a normal menopause 20 years ago.

On examination, the vagina was found to be somewhat constricted and shortened. The vaginal mucosa was thin, shiny, and yellowish in color, except for many small superficial hemorrhagic areas. A biopsy was taken and the patient was given 100 rat units of amniotin intramuscularly, four times weekly (Fig. 3, a).

A second biopsy was taken on July 27, 1934 (Fig. 3, b). At this time the mucosa had regained some of its normal elasticity, appeared smooth, and no petechial hemorrhages were present. The patient volunteered that she was feeling better than she had in years. The treatment was discontinued for 4 weeks, after which she again returned. On examination considerable regression of the improvement and a few petechial hemorrhages were noted, although the patient had no complaints. Amniotin treatments were again instituted and continued for 6 weeks.

The third biopsy was taken on November 23, 1934 (Fig. 3, c). The patient's condition was markedly improved. She has been symptom free since the last course of treatments.

CASE 4. A. P., Unit No. 112262, aged 48 years, was first seen on September 17, 1934, complaining of an offensive, irritating vaginal discharge, dyspareunia, burning on urination, and pelvic discomfort. Local applications of various drugs and douches gave no relief, and the condition grew progressively worse. Radiation treatments for fibromyomas were given 2½ years ago, which produced an artificial menopause.

On vaginal examination the mucosa, particularly at the introitus, was found to be inflamed and glistening. Multiple petechial hemorrhages and superficial ulcers were present. A biopsy was taken and 100 rat units of amniotin were given hypodermically three times each week and one suppository nightly (Fig. 4, a).

On October 12, 1934, the patient stated that she felt better than she had in years. The mucosa appeared entirely normal. A second biopsy was taken and amniotin treatments continued (Fig. 4, b).

The patient returned for examination on November 23, 1934, and had no complaints. The mucosa was normal in appearance. Further treatments were discontinued.

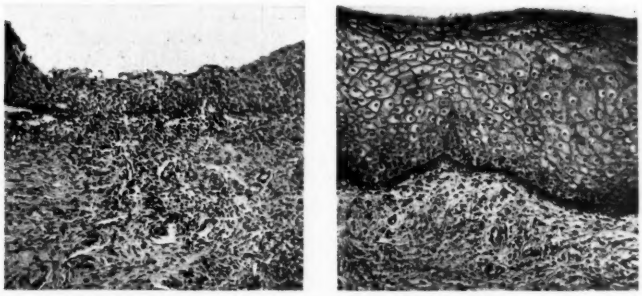
CASE 5. L. G., Unit No. 30968, aged 49 years, was first seen on November 21, 1930, complaining of profuse vaginal discharge for the past 3 months. She had a spontaneous menopause 3 years ago. There was a generalized inflammation of the introitus and the vagina, so that examination was painful. Speculum examination showed the vaginal mucosa to be smooth, glistening, and atrophied. Hanging-drop examination of the discharge was positive for Trichomonas vaginalis. Local treatment gave only temporary relief and the discomfort, burning, and vaginal discharge continued.

A biopsy was taken on October 3, 1934, and 100 rat units of amniotin were given hypodermically three times per week. Vaginal suppositories were ordered nightly (Fig. 5, a).

A second biopsy was taken on October 24, 1934 (Fig. 5, b). The patient's condition showed marked improvement. Hanging-drop examination was negative for Trichomonas. After 6 weeks, the treatment was discontinued and the patient has had no complaints to date.

EVALUATION OF STUDY

The vaginal mucosa is under the influence of the ovaries. Cyclical changes in the monkey have been described in a previous communication. Similar cyclical changes dependent on ovarian activity in the human female have been reported by Papanicolaou. This cyclical activity disap-



a b

Fig. 5. a, Note the small compact cells of the atrophic squamous epithelium and the moderate infiltration of round cells in the subepithelial zone.

b, Three weeks after treatment. Note the orderly arrangement of the basal cells, the large clear cells of the basalis, and the development of the functionalis. The inflammatory cells and subepithelial connective tissue have disappeared.

(All photomicrographs were magnified 42.5 times for accurate comparison of the squamous epithelium.)

pears following the menopause and the mucosa slowly atrophies so that it consists of only several layers of inactive cells. Allen castrated monkeys and followed these retrogressive changes in the vaginal mucosa. In our study, we were able to rebuild the atrophic vaginal mucosa in a monkey castrated over a year in 2 weeks' time with estrogenic hormone. Dierks recently reported that he produced a good functional layer in the vaginal mucosa of a castrated young woman with very large doses of estrogenic substance.

The theory upon which the present treatment was commenced was that the changes in senile vaginitis would disappear if the mucosa could be restored to the type present during active sex life. This would lead to the healing of the superficial ulcerations in the mucosa, the rapid disappearance of inflammatory changes, and the subsequent cessation of adhesive processes. The amount of estrogenic substance necessary could be determined only by careful study of the patients and repeated histological examination of the mucosa. The small amount of estrogenic substance required for a complete restoration of the normal mucosa and the rapidity of action was a distinct surprise. The marked responses of the atrophic epithelium to the dosage used made the present therapy easy and entirely feasible.

The changes in the vaginal mucosa as a result of treatment with estrogenic substance are indeed interesting. The inactive basal cells rapidly begin to proliferate and abundant mitoses can be seen in them. The number of cells in the basalis rapidly increases. They exhibit all the signs of active growth. Under continued stimulation the basalis develops a good functional layer and the typical zone of intra-epithelial cornification can be seen. The cells soon contain an abundance of glycogen.[1] The inflammatory foci beneath the squamous epithelium usually seen in senile vaginitis disappear. A marked increase in the vascularity of the submucosa likewise occurs. All of these striking changes can be followed accurately in the photomicrographs which are all of the same magnification, so that proper comparisons may be made.

The patients show improvement within a few days after treatment, and in most instances their symptoms have all disappeared in about 10 days. A general feeling of well-being is usually present and some of the elderly women insist that they feel better than they have in years. Grossly, the changes are quite apparent. The mucosa becomes somewhat velvety, more elastic and more distensible. All signs of inflammation and irritation disappear. Petechial hemorrhages, superficial ulcerations, and filmy adhesions likewise disappear and the discharge stops.

These changes, however, are not permanent. Several weeks after the cessation of treatment, the mucosa rapidly returns to its previous atrophic condition. Within 4 to 6 weeks the usual senile mucosa is again present. However, the patient's symptoms do not return, unless she has not received enough treatments and some inflammation still remains. If she has been treated for a sufficiently long time so that the mucosa has healed completely and all subepithelial inflammation has disappeared, then the symptoms do not return

[1] A complete histological study of the glycogen changes in the vaginal epithelium, upon which the hydrogen-ion concentration and bacterial flora depend, will be reported later.

until those factors which produce senile vaginitis again are present. If trauma and infection are again introduced, senile vaginitis will undoubtedly recur. In our series it was found that the patients should be treated for a period of 4 to 6 weeks. The patients with marked changes should be treated for 6 to 8 weeks. In all of our cases the results were good, the symptoms all disappeared and remained cleared up for at least 6 months, during which time the patients were carefully followed. This sequence of events demonstrates conclusively that the physiological changes in the vaginal mucosa in themselves do not produce symptoms. If trauma and infection are introduced, senile vaginitis develops.

In some of our cases the patients were treated for Trichomonas vaginitis for a considerable length of time. These were the most stubborn and difficult cases because they did not respond to the usual therapy for this condition. A few of these cases were treated with estrogenic substance and to our surprise they cleared up rather promptly. Undoubtedly, the difficulty in eradicating the infection was due to the fact that the mucosa was so atrophic. A restoration of the mucosa to the normal adult type seen during active sex life caused a prompt disappearance of the organisms. It is likely that the organism itself was only an accidental finding and may have played little or no rôle in the causation of the symptoms. It is therefore suggested that in the treatment of Trichomonas vaginalis vaginitis occurring in the postmenopausal period an estrogenic substance should be used as an aid to whatever therapy is desired.

SUMMARY

The treatment of senile vaginitis heretofore has been extremely unsatisfactory. The use of an estrogenic substance, amniotin (Squibb), rapidly restores the normal adult epithelium seen during active sex life. The simple restoration of the epithelium leads to a healing of the ulcerated areas, a disappearance of the inflammatory symptoms, a cessation of the adhesive manifestation, and a complete disappearance of all symptoms. No undesirable effects have been noted nor can they occur during the postmenopausal period. Although the vaginal mucosa reverts to the normal senile type the symptoms do not recur. Interesting biopsy specimens showing all the changes initiated by the estrogenic substance in the vaginal mucosa are presented. The treatment is simple, inexpensive, and entirely feasible. The biopsy method of study can be used as an aid in all endocrine studies in the human female.

I wish gratefully to acknowledge the co-operation of Dr. J. J. Durrett and Dr. J. A. Morrell of E. R. Squibb and Sons, and the liberal supply of amniotin which they furnished for this study.

REFERENCES

ALLEN, EDGAR. The Menstrual Cycle of the Monkey Macacus Rhesus. Contrib. to Embryology No. 98, Carnegie Inst. Wash., Pub. 380, vol. 19, pp. 1–44.

DAVIS, M. EDWARD, and HARTMAN, CARL G. Changes in vaginal epithelium during pregnancy in relation to the vaginal cycle. J. Am. M. Ass., 1935, 104: 279.

DIERKS, K. Normal monthly cycle of human vaginal mucosa. Arch. f. Gynaek., 1927, 130: 146.

Idem. Experimentelle Untersuchungen an menschlicher vaginal Schleimhaut. Arch. f. Gynaek., 1929, 138: 111.

LEWIS, ROBERT M. Study of effects of theelin on gonorrheal vaginitis in children. Am. J. Obst. & Gynec., 1933, 26: 593.

PAPANICOLAOU, G. N. Sexual cycle in human female as revealed by vaginal smears. Am. J. Anat. (supp.), 1933, 52: 519.

Idem. Diagnosis of early human pregnancy by the vaginal smear method. Proc. Soc. Exper. Biol. & Med., 1925, 22: 436.

FERRIC CHLORIDE COAGULATION IN TREATMENT OF BURNS

With Résumé of Tannic Acid Treatment

GLENN L. COAN, M.D., F.A.C.S., Wyandotte, Michigan

THE record of ten years of treatment of burns by coagulants has firmly established the principles enunciated by Davidson (5), when he introduced tannic acid as an external application in 1925. The work recorded here was stimulated by the success of his treatment, together with the belief that some other preparation might be found better than tannic acid.

Davidson (6, 7, 8) attacked the problem in the field of physiology, pathology, and biochemistry, consolidated the experimental work of others, added many observations of his own, and evolved a completely rational outline of burn treatment for the first time in medical history. It may well be said that his work bears the same relation to modern management of burns, as that of Lister to modern surgery. In that connection it will be recalled that the surgical principles, demonstrated by Lister, have perpetuated his memory long after phenol sprays and solutions disappeared from operating rooms. In a similar way, Davidson will be remembered because of his declaration of the principles of coagulation treatment, even though tannic acid may be displaced by other materials as an external application. In other words, tannic acid, itself, seems to be a comparatively minor factor in the socalled "tannic acid treatment."

We recognize a marked reduction in mortality and morbidity since the popularization of primary coagulation. Beck and Powers, Seeger, Glover, and Wells have contributed valuable suggestions in modifying the original technique. The work of Penberthy and Weller, especially in the surgical treatment of late complications, makes possible the rehabilitation of many apparently hopeless cases. Beekman noted a mortality percentage almost cut in half. From other countries, notably England (23) and Austria (24) come reports of decreased mortality and morbidity in recent years. McClure and Allen (13) have recently presented convincing statistics, establishing the value of tannic acid.

Davidson summarized the advantages of the tannic acid regimen as follows: (1) it lessens toxemia, (2) is analgesic, (3) minimizes trauma, (4) conserves body fluids, (5) limits secondary infection and consequent scar formation, and (6) forms scaffold for growth of young epithelial cells. Each statement remains unchallenged after years of clinical trial.

OBJECTIONS TO TANNIC ACID

1. Instability of solutions. Glover (9) called attention to the rapid oxidation of tannic acid to the darker, more irritating gallic acid, after a few days' exposure to light and air. The preparation of fresh solutions seems imperative; the marketing of prepared jellies, and the storage of stock solutions in hospitals and physicians' offices seem equaliy illogical.

2. Stiffness of coagulum. This may cause too early splitting, or loosening at the edges, with defeat of the main purposes of coagulation. In the region of a joint, early mobilization may be prevented, and functional recovery thereby retarded; or the patient's conscious or unconscious movements may loosen the eschar too early, with resultant infection and excessive scarring. Lock (11) warned against the use of tannic acid around the circumference of a finger, because of the danger of gangrene after the digit swells.

3. Necrosis and infection under coagulum. Aldrich remarked that it is difficult to discover infection under a tannic eschar until it is very extensive. In my experience infection tended to burrow and spread under tannic coagulum rather than localize.

4. The time factor. This affects results in two ways. In the first place, a material which can be depended upon to coagulate more rapidly, would erect a more dependable barrier against infection. In the second place, where the average tannic eschar requires removal in 2 weeks or less, a coagulum which could be depended upon to hold for a longer period, would give the new epithelial cells more time to consolidate the reparative process, especially in third degree burns. It follows logically that in many cases, skin-grafting might thereby be avoided.

USE OF OTHER COAGULANTS

Seeger claimed improved results by neutralizing tannic acid solutions with sodium carbonate to approximate a hydrogen-ion concentration of 7.0. He has also worked in conjunction with chemists in the tanning industry, on other coagulants in the tannin group. Aldrich has used gentian violet and other dyes, which coagulate proteins slowly,

Fig. 1. Case 1. Leg, showing extent of voluntary motion of knee. At left, note crinkling of coagulum on fifteenth day; at right, the epithelialization on twenty-fourth day. The dark areas at the right were injured by too early removal of coagulum, and recoagulated with mercurochrome.

Fig. 2. Case 1. Hand, showing appearance of coagulum on fifteenth day, and after its removal on twenty-fourth day.

stressing their value as antiseptics. Shillito suggested silver nitrate solutions, ionized by exposure to ultra-violet light; I tried this method once, obtaining a very hard coagulum, with a good end-result in a small third degree burn. Bettman recently urged the use of 10 per cent solution of silver nitrate, following tannic acid, claiming a more flexible coagulum, and more rapid coagulation. Stammel commented on the use of gallotannate of iron (black ink) by Filipinos for at least two or three generations; he remarked about surprising recoveries in 2 cases observed by him.

FERRIC CHLORIDE—RATIONALE

My interest in ferric chloride was aroused by a case encountered in 1929, a man burned by immersion in a vat of actively boiling ferric chloride solution. The impressive features of the case were: (1) primary coagulation by the chemical itself, without any other external treatment; (2) flexibility of the coagulum, permitting fair motion of all joints; (3) comfort of the patient, in spite of deep, extensive involvement of both legs up to the mid-thigh level; and (4) an excellent end-result, with 100 per cent functional recovery in 3 months, in spite of the fact that I unwittingly removed the coagula much too early.

No animal experimentation was attempted, because of the dissimilarity in the reaction of hairy animals, as compared with burned human skin. More recently a few comparative observations have been made, by applying various coagulants to the areas from which skin-grafts have been taken, studying the effect of different agents on the same individual. Proceeding cautiously, first only with minor burns, later with those of greater extent and depth, a series of over 140 cases was observed with several physicians.

Some precedent for the use of ferric chloride was found in the literature. I had seen the remarkable relief and rapid recovery of sufferers from dermatitis venenata (ivy poisoning) under ferric chloride treatment, as proposed and rationalized by McNair. Slack had reported the use of tincture of ferric chloride on burns as far back as 1891, and John B. Murphy had commented favorably on the treatment. There was no evidence that anyone had given the preparation intensive study or extensive trial, probably because the advantages of coagulant treatment were not recognized prior to Davidson's work.

Slack claimed the following merits for ferric chloride: (1) it relieves pain promptly in 5 minutes, (2) forms a dry surface, requiring no dressings, (3) prevents infection, (4) heals quickly, with little scar formation, and (5) is convenient, inexpensive, and easily applied. He failed to express the biochemical concepts, as did Davidson, but otherwise the similarity of their findings is striking.

CHEMISTRY AND PHARMACOLOGY

The U.S.P. solution and tincture of ferric chloride contain an excess of hydrochloric acid, which

is considered objectionable. By addition of increasing amounts of sodium hydroxide, a reaction occurs, represented by the formula $FeCl_3 + 3NaOH = Fe(OH)_3 + 3NaCl$, or intermediate stages by varying proportions of ferric chloride and ferric hydroxide, the latter being very soluble and fairly stable in solutions of the former. This makes possible a choice of solutions of variable hydrogen-ion concentration, ranging from 3.2 to 6.9, according to estimations made so far. After a week or two there may be some precipitation, but the supernatant liquid remains quite effective as a coagulant, and is less irritating than the fresh solution.

The transition from ferric chloride to the hydroxide, with the intervening theoretical compounds, and the dialysis of the colloidal hydroxide sol, form a fascinating chemical study, which need not concern us here, except to note that the hydroxide coagulates proteins, and solutions of ferric hydroxide in the chloride are just as effective as the chloride alone. Lunde and Wuelfert and Lindau have presented experimental data, measuring the coagulant effect of dialyzed ferric hydroxide sol.

Dialyzed iron (representing 5% Fe_2O_3) has been used in five relatively minor burn cases, with promising results. Coagulation is slower than with ferric chloride, but more rapid than with tannic acid. I believe it is the least painful coagulant that I ever used. Further observation is necessary before recommending its general use.

In most of the cases treated so far, we have used 5 per cent aqueous solutions, made by dissolving commercial anhydrous ferric chloride in distilled water, and filtering. This has been alkalinized in some cases by addition of sodium hydroxide. Solution of ferric chloride in glycerin has been used in 2 cases, but is not recommended. Our experience with tragacanth jelly has been too meager to draw any conclusions. The following solutions are useful, because they can be obtained easily at any pharmacy:

(1) ℞ Tincturae ferri chloridi 30.0
Sig: Paint over small, unbroken blebs.

(2) ℞ Tincturae ferri chloridi 15.0
Sodii hydroxidi 0.3
Aquæ destillatæ q. s. ad 30.0
Sig: Paint or spray over denuded surfaces.

TECHNIQUE

In technique of application, there is no essential difference between tannic acid and ferric chloride solutions. A pledget of cotton on a wooden applicator is sufficient to cover a small area. In more diffuse burns atomizers are preferred, my personal choice being a cheap metal type, such as those sold with insecticides, their low cost permitting rejection after use in one or two cases.

The primary pain of ferric chloride coagulation may be considerable, about the same as that noted in the use of tannic acid; but after 5 minutes there is the same secondary analgesic effect. Morphine or barbiturate analgesia is desirable, and in some instances nitrous oxide anesthesia, or preliminary local applications of butyn or nupercaine solutions may be preferable.

Potentially infected burns, in which coagulation has been delayed over 6 hours, have usually been prepared by preliminary sponging with gauze, moistened in sodium hypochlorite solution, which serves for both antisepsis and débridement. Clean burns, seen before meddlesome self-treatment, have been treated by aseptic débridement, and immediate coagulation of denuded surfaces. First degree burns, and those of second degree, showing only small, unbroken blebs, are simply painted with tincture of ferric chloride every 2 hours, with no dressing; later coagulation may or may not be necessary.

A coagulum should be left intact until it can be removed without exposing any bleeding surface, but any loosened portion should be cut away as a possible focus of infection. Then it may be desirable to apply some antiseptic, as a secondary coagulant, such as gentian violet, or an acetone-alcohol solution of metaphen or mercurochrome.

With an average second degree burn, the eschars may be removed with a dry underlying surface in 12 to 14 days; however, in several cases the coagula have been left undisturbed for over 3 weeks, with evident benefit from the prolonged protection of the healing surface.

Skin-grafting should be considered, if any wide, unhealed areas remain a week or 10 days after removal of the coagulum. Fortunately, it has not been indicated in any of our cases so far.

CASE RECORDS

A few cases are presented, illustrating a variety of problems, including the only fatal case in our series. The only cases not reported, in which ferric coagulation was not entirely successful, were small, infected burns, seen over 3 days after injury, where active infection contra-indicated the use of any coagulant. In such cases moist dressings (Dakin solution preferred) are probably the best solution of a difficult problem. Ointments have practically no place in burn treatment; infection is the inevitable result. The one exception to that rule has been superficial facial burns, treated with butesin picrate ointment.

CASE 1. A male laborer, aged 23 years, was admitted with second and third degree burns of entire dorsal surface of left hand, including all fingers, and entire circumference of left leg, including knee and popliteal space, caused by throwing a pail of toluol on an open fire (Figs. 1 and 2). Débridement with wet gauze (Dakin solution) was followed by a spray of 5 per cent aqueous solution of ferric chloride every hour for three applications. Eighteen hours later a few new blebs and the edges of the burns were treated in the same manner. By that time a firm, flexible, mahogany-brown coagulum had formed. Six days later after edema had subsided, these had become wrinkled, as shown in photographs, but still remained firm. Mobilization of all joints was urged from the eighth day, but the fingers could not be moved much until the fourth week. About 75 per cent of the coagulum was loose enough to be removed on the fifteenth day; that over the deeper burns was left until the twenty-third day. The entire surface was free from infection, excepting a small, walled-off pocket 2 centimeters in diameter over the third metacarpophalangeal joint. He was walking about the ward on the twenty-fourth day, and left the hospital on the thirty-first day. The patient removed five loose, charred fingernails on the date of discharge. The leg was considered normal on the fortieth day, with completely restored function of the hands and fingers after 60 days, at which time he returned to his usual work (Dr. J. G. Knapp).

CASE 2. A woman 6 months pregnant, aged 29 years, was burned by an explosion of naphtha while cleaning clothing, the entire body surface being involved, except the scalp and the soles of the feet. Gentle débridement with wet gauze was followed by spraying with 5 per cent aqueous solution of ferric chloride. A good, flexible coagulum was obtained, and the patient was remarkably comfortable after the first 12 hours. A stillborn fetus was delivered 48 hours after admission, collapse ensuing, with death 3 hours after delivery. Mentally alert and rational until after delivery, this case is an example of simplification of nursing care, providing maximum comfort following an inevitably fatal burn (Dr. E. H. Engel).

CASE 3. A man aged 29, husband of patient, Case 2, suffered second and third degree burns of the entire surface of both hands and wrists, incurred in his effort to extinguish the fire. Good coagulation was obtained 18 hours after the first application of ferric chloride. His mental condition was agitated during the first few days, incident to the shock of the accident and his wife's death, with a background suggesting an acute alcoholic psychosis. His maximum temperature was 101.8 degrees F., with recession to normal on the fifth day, when he was transferred to another hospital. There his coagula were forcibly removed under ether anesthesia on the fourteenth day, the propriety of this procedure being questionable. He returned under our observation 4 days later, with small granulating areas on the flexor surfaces of the fingers. On the twenty-sixth day these had healed, and function of the hand was estimated over 90 per cent. On the thirty-fifth day, function was 100 per cent, and he was piloting an aeroplane.

CASE 4. A 3 year old boy was rescued by firemen from a burning shed, where there appeared to have been an explosion of oil of turpentine, causing deep second degree burns of the dorsal surfaces of both hands, all fingers, neck, left cheek, both ears, nose, forehead, and scalp. The child was taken to the hospital, but was removed by his father, and treated at home with one of the many pernicious proprietary ointments. When seen on the third day, the bandaged areas were discharging, new blebs were filled with purulent fluid, and lesions of impetigo contagiosa were appearing on his leg and abdomen. Two brothers were found to have impetigo. His temperature was 102.6 degrees F., but pleas for hospitalization were unavailing. Under barbiturate analgesia, antiseptic débridement with dakinized gauze, and coagulation with 5 per cent solution of ferric chloride in 50 per cent alcohol were carried out over all burned areas, except the scalp. Good coagula formed in about a half-hour. After clipping the hair, ointment of ammoniated mercury was ordered for the scalp and the impetigo lesions. I was pleasantly surprised by the course of the burns. The temperature was never found above 101 degrees F., the child appeared to be comfortable, and the coagula held remarkably well. From the seventh to tenth day, portions of the eschars were trimmed away from the left hand, neck, and forehead, because of infection beneath; and secondary coagulation with alcohol-acetone solution of metaphen was done. Over two-thirds of the involved area healed without evidence of infection. The only appreciable scar was about 1 centimeter in diameter on the forehead close to the hair line. On the seventeenth day the last coagula were removed. The temperature had been normal after the eleventh day, and recovery was considered complete on the twenty-fifth day. Albuminuria was noted only on the day following coagulation. This was a particularly trying case, and admitting the element of good fortune, the result was far better than the normal expectation.

CASE 5. A male laboratory technician, was burned by explosion of a flask, containing an inflammable mixture of phenol and trimethyl carbinol, $(CH_3)_3COH$, his entire back being burned from the occiput to the level of the iliac crests. The phenol presented an element of danger, fatal cases having been reported due to absorption through burned skin. Within a half-hour 5 per cent alcoholic solution of ferric chloride was applied to the burned area; a black, inky stain, suggesting the presence of phenol, appeared at once. At the hospital 18 hours later, débridement and coagulation were done, the denuded area covering about 2,500 square centimeters. On the third day the temperature reached 104 degrees F., the patient was semidelirious, and albumin and casts were found in the urine. About 20 per cent of the burned area required recoagulation on the fifth day, probably because it was impossible to keep the patient from moving about, and lying on his back. The temperature and urinalysis were normal after the eighth day; the coagula loosened on the tenth to thirteenth day; recovery was considered complete on the twenty-fourth day, when he returned to work. Later examinations indicated that his acute nephritis had cleared completely (Dr. J. G. Knapp).

It is noteworthy that in the chemical industry, tincture of ferric chloride is considered a better antidote in phenol burns than alcohol alone, a blue-black, inky, non-toxic iron salt, possibly a tannate, being formed.

CASE 6. A chemist, aged 30 years, was burned about the hand and forearm, involving both the wrist and elbow, by a splash of liquid anhydrous ammonia from a broken flask. It was treated primarily by application of tincture of ferric chloride to the unbroken skin every 2 hours. After 18 hours several large blebs were opened, and the denuded surfaces, approximating 350 square centimeters were coagulated with the 5 per cent aqueous solution. This was complete in a half-hour. His maximum temperature was 99 degrees F.; he was comfortable, with good motion of involved joints; and returned to light work of his own volition after 7 days. The coagula were allowed to loosen spontaneously, this occurring in from 14 to 20 days. Recovery was complete by the time this was finished.

CASE 7. A moulder, 50 years old, suffered second and third degree burns from a splash of molten brass, involving the left middle finger, wrist, dorsal surface of left forearm, elbow, and lower third of upper arm. He was first seen 18 hours after the accident. Because of the delay in treatment, a moist dressing (Dakin solution) was applied for an hour before coagulation, which was done with 5 per cent aqueous solution of ferric chloride. Coagula were firm, flexible, and tenacious, with free motion of involved joints. There was no appreciable rise of temperature, and healing was complete upon removal of loose eschars between the ninth and eighteenth day, according to the depth of the burns. He was at work on his usual job on the twenty-sixth day.

CASE 8. A male laborer, aged 26 years, was scalded by boiling water, causing second degree burns of the dorsal surfaces of the toes and left foot, ankle and leg up to the knee. This was treated 6 hours after the accident by aseptic débridement, followed by application of a 2 year old solution of ferric chloride (5 per cent aqueous), with similar treatment of new blebs and edges of burns after 24 hours. Coagulation was complete after 2 hours; the maximum temperature was 99 degrees F.; there was no discomfort after the first night. The patient left the hospital on the fourth day, and was walking about the house on the seventh day, without permission. The coagulum was firm, but pliable, wrinkling to adjust itself to movement of the ankle in walking. It was removed easily on the fourteenth day, with healing complete except for one small area (2 by 3 centimeters) which bled. That was my error; only loose coagula should be removed. There was no evidence of infection at any time, and the patient returned to work on the twenty-ninth day.

CASE 9. A male infant, 13 months old, was scalded by overturning a kettle of boiling water. Two relatively superficial second degree burns of the abdomen and right thigh (240 square centimeters) were coagulated by bandaging for 12 hours with 5 per cent tannic acid jelly. Denuded areas on the penis, scrotum, left thigh, knee, leg, ankle, foot, and toes were immediately coagulated by ferric chloride, two applications of the aqueous solution being required an hour apart. The ferric-treated area approximated 1,200 square centimeters. The maximum temperature was 101.4 degrees F., with no fever after the fourth day. From the second day, when a few new blebs were opened for coagulation, until the ninth day, no local treatment or any sedative was necessary. Then tannic coagula, and the ferric eschars over a similar burn on the left thigh were removed, showing dry epithelialized surfaces underneath. The more deeply burned areas on the foot and leg were exposed between the fourteenth and nineteenth day. All surfaces were dry with no crusts or scarring, excepting a keloid-covered area 3 centimeters in diameter, found on his ankle 6 months later. Recovery was considered complete on the twenty-third day. In this case the tannic jelly gave an excellent result, but ferric chloride, given a much more severe test, showed equally good results, with more flexible coagula.

CASE 10. A male laborer, aged 26 years, was also scalded by boiling water. Five per cent solution of tannic acid was applied to a denuded surface (250 square centimeters) on the outer aspect of the right thigh, while 5 per cent aqueous solution of ferric chloride was used on a similar area on the right arm and forearm, involving the elbow. The ferric coagulation was complete within an hour after two applications; that with tannic acid required eight applications over a period of 24 hours. Subjectively, the pain of each application was reported about the same, with the advantage in favor of ferric chloride, because coagulation was more rapid. The ferric coagulum was flexible enough to permit fair motion of the elbow, with crinkling over the arm as the edema subsided, and the joint was moved, but without loosening until healing was complete. On the seventh day the tannic coagulum had split horizontally, and was loose at the edges. Both were removed on the fifteenth day, with equally excellent end-result. As a single instance, with ferric chloride given the more severe test, it was more satisfactory than tannic acid.

EVALUATION OF RESULTS

In general, where the burn is not deep, and does not involve an area about a joint, when coagulation is done promptly, with slight possibility of infection, there is little or no difference in the relative merit of tannic acid and ferric chloride solutions. However, the following comparisons are indicated by the observations so far:

1. *Stability of solutions.* Tannic solutions become irritating in a short time; those of ferric chloride precipitate basic iron salts slowly, but the solution remains effective and rather less irritating. (In Case 8, a 2 year old solution was quite effective.)

2. *Consistency of coagulum.* That of tannic acid has been likened to sole leather, that of ferric chloride to top leather, of varying thickness, according to the depth of the burn. Early mobilization of joints is usually possible without disturbing a ferric coagulum; in my experience, this has not been possible with tannic acid.

3. *Necrosis and infection.* These complications are considered jointly, because both are invariably present when either occurs. The principal difference is that with ferric chloride, infected or necrotic areas have been small, localized lesions, rather easily detected by palpation, while under tannic coagula, I have been able to discover them only after burrowing and spreading, and draining at the edge.

4. *Staining of skin.* This deserves consideration because Pusey has reported brown stains of the skin after the use of wet dressings of ferrous sulphate solution, and electric burns in the presence of iron have been known to leave a brownish-black deposit in the skin (25). Among 52 traced cases, the only stain noted followed a phenol burn, presented a light-brown freckled appearance. Since phenol burns are prone to leave stains (brown, reddish brown, or purplish, 25) the use of ferric chloride was not considered the cause of the stain. At first we hesitated to use it on the face, but more recently it has been applied to the face, forehead, and eyelids. The chemical, of course, is removed with the coagulum. The solution is easily removed from the hands by rinsing in clear water, or a weak acetic or citric acid solution.

5. Staining of linen. Hospital executives have complained because iron stains are not removed in ordinary laundering. The best decolorizing agent is a solution of potassium fluoride, with an excess of hydrofluoric acid; after decolorizing the spots, clear water is used for rinsing; the fluoride solution should not be used on the hands. This solution is available at any laundry supply house.

6. Tenacity of coagulum. Ferric coagula have been removed in good condition as late as the twenty-third day; serviceable tannic coagula are seldom seen after the fifteenth day. With ferric chloride we see wrinkling of the coagulum with movement of joints, and after swelling subsides, without any loosening. In my opinion, this is the greatest advantage of ferric chloride over tannic acid.

SUMMARY

1. Solutions of ferric chloride, used in coagulating burns, show the same advantages as tannic acid, with certain definite points of superiority, especially in providing for early mobilization of joints.

2. Further clinical work with ferric salts is desirable. More extensive study of the hydrogen-ion concentration values of the various chloride-hydroxide solutions is planned, also further investigation of the clinical possibilities of colloidal ferric hydroxide, alone and in solution with ferric chloride.

3. The general condition of the burned individual transcends in importance the choice of external application. However, early coagulation of denuded surfaces must be regarded as an important factor in treatment, and an essential factor in achieving the best results in diffuse burns.

REFERENCES

1. Aldrich, R. H. The rôle of infection in burns. New England M. J., 1933, 208: 299.
2. Beck, C. S., and Powers, J. H. Burns treated by tannic acid. Ann. Surg., 1926, 84: 19.
3. Beekman, F. Tannic acid treatment of burns. Arch. Surg., 1929, 18: 803.
4. Bettman, A. G. Tannic acid silver nitrate treatment of burns. Northwest Med., 1935, 34: 37.
5. Davidson, E. C. The use of tannic acid in the treatment of burns. Surg., Gynec. & Obst., 1925, 41: 202.
6. Idem. The prevention of toxemia in burns. Am. J. Surg., 1926, 40: 114.
7. Idem. Sodium chloride metabolism in cutaneous burns. Arch. Surg., 1926, 13: 262.
8. Davidson, E. C., and Matthew, C. W. Plasma proteins in cutaneous burns. Arch. Surg., 1927, 15: 265.
9. Glover, D. M. Six years of tannic acid treatment of burns. Surg., Gynec. & Obst., 1932, 54: 708.
10. Lindau, G. Ueber die Einwirkung von Eiweiszstoffen auf Eisenhydroxydsol. Biochem. Ztschr., 1930, 219: 385.
11. Lock, N. Treatment of burns. Clin. J., 1933, 62: 200.
12. Lunde, G., and Wuelfert, K. Ueber die Faellung von Eiweisskoerpern mit Eisenhydroxydsol. Biochem. Ztschr., 1930, 219: 171.
13. McClure, R. D., and Allen, C. I. Davidson tannic acid treatment of burns: ten year results. Am. J. Surg., 1935, 28: 370.
14. McNair, J. B. Contribution to chemotherapy of rhus dermatitis and tentative method of treatment. Arch. Dermat. u. Syph., 1921, 3: 802.
15. Murphy, J. B. Practical Medicine Series, 1915, vol. 2, 94.
16. Penberthy, G. C., and Weller, C. N. Complications associated with the treatment of burns. Am. J. Surg., 1934, 26: 124.
17. Pusey, W. A. Stains in skin. J. Am. M. Ass., 1917, 78: 627.
18. Seeger, S. J. The hydrogen-ion concentration value of tannic acid solutions used in the treatment of burns. Surg., Gynec. & Obst., 1932, 55: 455.
19. Shillito, L. Ionized silver in treatment of burns. Brit. M. J., 1929, 2: 668.
20. Slack, H. R. New treatment of burns. J. M. Ass. Georgia, 1916, 5: 153.
21. Stammel, C. A. Empiric use of ink in burns. J. Am. M. Ass. 1929, 93: 1164.
22. Wells, D. B. The aseptic tannic acid treatment of diffuse superficial burns. J. Am. M. Ass., 1933, 101: 1136.
23. Wilson, W. C. The tannic acid treatment of burns. Sp. Rep. Series, 141. Privy Council, Medical Research Council, H. M. Stationery Office, London, 1929.
24. Vienna Letter. J. Am. M. Ass., 1934, 192: 632.
25. Burns of skin with brown discoloration, (ans. to query), J. Am. M. Ass., 1929, 93: 1672.

MASSIVE RESECTION OF THE SMALL INTESTINE

An Analysis of 257 Collected Cases

H. E. HAYMOND, M.D., Midwest, Wyoming
From The Department of Surgery, The University of Chicago

FOR many years the term "extensive" when applied to resections of the small intestine has been indicative of the removal of lengths measuring 200 centimeters or more. This limit had been chosen early in the literature on resections, because it was estimated that such a length constituted approximately one-third of the small intestine, and represented, according to the experiments of Senn in 1888, the extent of the small bowel that might be removed from a given patient with safety.

It must be agreed that the surgical removal of large amounts of the intestine is not usually an elective procedure, for the surgeon is confronted at operation with the alternative of allowing the patient to die or resorting to a heroic effort to save the individual by resection.

HISTORICAL

Perhaps the first massive resection of the small intestine was done by Koeberle in 1880 when he removed 205 centimeters. The patient recovered. Before 1900 additional cases had been reported by Obalinski, Fantino, Ruggi, Shepherd, Schlatter, Dreesmann, Monprofit, and Franz. Collections of cases have been made by Schlatter (1906), Storp (1907), Soyesima (1911), Flint (1912), Flechtenmacher (1917), Cannaday (1919), Watson (1923), Brenizer (1929), and Dorow (1932). Dorow's case and his collection from the literature brought the total number of cases of massive resection of the small intestine to 97.

The present study consists of the reports of 3 cases and an analytical study of a total of 257 collected cases. In each instance, so far as was possible, the original reference was consulted. In reviewing the collected series of the various authors, a number of duplications have been eliminated in which the author of the article was other than the surgeon who performed the resection. A number of examples of shortcircuiting operations or exclusions of the small intestine as reported by Brohee, Ghedini, and Van Verts have been eliminated from the present study. Among his 83 cases, Brenizer has included Jackson's case of successful resection of 142 centimeters in a male infant of two; this is, undoubtedly, a massive resection of small intestine for a patient of such an age, but it is not included in the present study. A number of collections have credited Kouwer with a resection of 224 centimeters, whereas this particular case was reported by Friele. One collector has included Boeckel's case in his series of extensive resections, but this is an error inasmuch as a review of the original reference shows there was a resection of 80 centimeters of ileum and 90 centimeters of colon.

The earlier collections have given the impression that there is a fairly high percentage of recovery, and that good functional results in extensive resection can be expected. They all have guarded the apparent good results with the statement that undoubtedly only the good results are apt to be reported in the medical literature. Flint recorded 48 recoveries in 59 cases; Flechtenmacher, 50 recoveries in 57 cases; and Cannaday noted 60 recoveries in 69 cases. Brenizer found a mortality of only 14.3 per cent in 83 cases with good functional results in 65.5 per cent of his series. Dorow reported a mortality of 18.6 per cent in his series of 97 cases.

LENGTH OF THE SMALL INTESTINE

Inasmuch as the length of the small intestine varies with each individual, it must be remembered that a resection of a large amount in one individual would constitute a different percentage of the total length than in another, and if all other factors were equal, it is probable that different results might be obtained in 2 patients. The opinion expressed by the majority investigating intestinal lengths is that the length in the adult female is somewhat less than in the male. Some observers contend that negroes, Russians, and races living primarily on a coarse diet are inclined to have longer intestinal lengths. Lamb reported a negro with 1,216 centimeters (40 feet) of small intestine. Bryant found that the small intestine varied from 10 feet (304 cm.) to 28 feet 4 inches (863 cm.) with an average of 20 feet 6 inches (614 cm.) in 160 adults. Beneke states there is a definite relationship between body length and intestinal length, and that for slender, average, and stocky individuals, there is an average of 389 centimeters of small intestine per 100 centimeters of body length. Wallenius is quoted by Kallio as having measured

the intestinal length in 212 Finnish patients and found an average of 760 centimeters. Kallio reviewed the reports of Meckel, Rolssen, Richter, Treves, Robinson, Tarenetsky, Dreike, Kubo, Chudzinsky, Giacomini, and Wallenius. The reports mentioned when added to the 14 observations of Miyake and the 31 cases of the author's series in which the total small intestinal length was noted at operation or necropsy makes a grand total of 1,161. These 1,161 cases had an average intestinal length of 21 feet 6 inches (657 cm.).

CASE REPORTS

The 3 cases to be reported here include a careful metabolic study of the 1 case that survived operation.

CASE 1. H. D. (A. M. B. H. No. 31940), aged 41 years, a white American male, a truck driver, was crushed between a 2 ton steel beam being lifted by a steam crane and the rear wheel of his truck. The main impact came on the left loin, and almost immediately the patient was unable to move because of severe abdominal pain. Less than 1½ hours after the accident on May 14, 1930, the abdomen was opened by Dr. W. T. Harsha at the Illinois Central Hospital under ether anesthesia. The peritoneal cavity was distended with a large amount of fresh blood, the root of the mesentery of the entire ileum was found torn at its abdominal attachment and was bleeding profusely. The bleeding points were caught and ligated. There were tears in the sigmoid and mesosigmoid and these were repaired. The ileum was excised well beyond the lines of demarcation of the disturbance of its blood supply from approximately the jejunal junction to about 8 centimeters short of the ileo-cecal valve. Because these two ends could not be approximated for an end-to-end anastomosis, the distal end of the jejunum was brought through a stab wound in the left rectus so as to establish a fistula, and the end of the ileum was inverted. The abdomen was closed. The total length of the bowel measured within 2 hours after removal was 383 centimeters (12 feet 7 inches).

Immediately after operation, he was given 520 cubic centimeters of whole blood intravenously. On the third day after operation, drainage from the jejunal fistula stopped, but this soon discharged material again after the relief of an acute dilatation of the stomach. For the next 2 weeks the patient received 2,100 to 3,975 cubic centimeters of physiological saline parenterally.

On May 23, under local anesthesia, a lateral anastomosis was made between the jejunum and the middle of the transverse colon through a window in the omentum. The jejunal stoma was supposedly about 12 inches from the fistulous end. The peritoneum was closed without drainage. The recovery from the second operation was rapid. The drainage from the fistula continued to be profuse, and all attempts to close the opening by means of strapping with adhesive and packing the tract with gauze were unsuccessful.

On October 11, the jejunal fistula was closed, the postoperative course was entirely uneventful, and the wound was healed at the time of his discharge from the hospital on November 10, 1930.

On December 15, he was admitted to Billings Hospital on the service of Dr. L. R. Dragstedt for metabolic study. At the time of his admission he had lost 100 pounds since his operation 7 months before. His loss of strength was proportionate with his loss of weight. Since the enterectomy he had had an average of four yellowish watery stools daily. The day following his admission, further X-ray examination of the gastro-intestinal tract was carried out. Two hours after ingestion of barium, the head of the column was noted in the transverse colon, and at the end of 4 hours it had reached the rectum. Also, at the end of 4 hours, it was noted that most of the opaque meal was in the transverse colon and in a very dilated ileum. Twenty-four hours after the barium had been given, extreme dilatation of a loop of the ileum in the left side of the pelvis was noted.

The patient was discharged on February 19, 1931, after a careful study had been made of his powers of assimilation. He weighed about the same at the time of his dismissal as he did on admission to the hospital despite the fact there had been some diminution in the number of daily stools on a high carbohydrate, high protein, and low fat diet.

The patient was re-admitted to the Illinois Central Hospital on March 10, 1931, and died 2 days later of peritonitis. The history suggested that the condition had been present for about a week.

A necropsy was performed by Dr. H. G. Wells of the Department of Pathology, University of Chicago. The body was that of an emaciated man of 41. The most significant pathological findings were limited to the gastro-intestinal tract. The jejunum was found to be anastomosed to the transverse colon 55 centimeters from the duodeno-jejunal junction. The jejunal mucosa of the first portion seemed normal. The blind end of the jejunum beyond the point of the anastomosis was also 55 centimeters long. Its content was somewhat thicker than that in the upper segment. The terminal 30 centimeters of the blind end was dilated to a diameter of 15 centimeters, and near the end of the stump were two fistulous openings into a pocket which apparently were the starting points of the peritonitis.

CASE 2. P. R. (A. M. B. H. No. 56877), aged 36 years, a housewife, was first seen in the Lying-In Dispensary of the University of Chicago Clinics on March 18, 1932. She gave a history of a dull pain appearing suddenly in the left upper quadrant on February 17, 1932, but she had no further distress until March 12. This attack was much more severe than the first, and it was accompanied by nausea and vomiting. After hospitalization, the patient's general condition became worse; nausea and vomiting were present along with abdominal pain and distention; and the leucocyte count mounted to 44,000 per cubic millimeter.

On the afternoon of March 24, 1932, the abdomen was explored by Dr. L. R. Dragstedt under novocain and ethylene anesthesia. The peritoneal cavity contained about 350 cubic centimeters of a serosanguineous fluid. The entire small intestine was distended with gas and was discolored; the discoloration ranged from black to purplish to dusky red. There was a definite line of demarcation in the lower ileum, but this demarcation was not as clean cut in the upper portion of the small intestine. The entire ileum, except a terminal few centimeters, and most of the jejunum were divided from a pulseless mesentery in one piece and the mass brought out through the lower end of the incision. After closure of the abdominal incision, a Payr clamp was applied, and 269 centimeters of partly gangrenous intestine were removed.

The patient was given a transfusion of 500 cubic centimeters of citrated blood and 700 cubic centimeters of saline immediately after operation. The next morning she felt fairly well, but at 9:30 a.m. she suddenly began to fail very rapidly, and died within an hour.

A necropsy was performed by Dr. Esmond R. Long of the Department of Pathology, University of Chicago. The

pathological findings included thrombosis of the mesenteric, celiac, splenic, hepatic, and left gastric arteries and their branches. This apparently resulted from embolism from a mural thrombus on an atheromatous plaque in the descending thoracic aorta.

CASE 3. M. K. (P. H. No. 156459), aged 40 years, a white American male, was admitted to the service of Dr. D. B. Phemister in the Presbyterian Hospital on May 30, 1922. The patient first complained of diffuse abdominal distress on the night of May 26, 1922; the pain continued throughout the next 3 days, and on May 30 it became more severe. Examination revealed an acutely ill man who had diffuse tenderness throughout the abdomen with somewhat greater tenderness on the right side. The leucocyte count was 17,500.

Operation was performed at 7:30 p.m. on May 30, by Dr. Phemister. The abdomen was opened through a lower right rectus incision. There was a gush of about 3 liters of straw colored clear fluid as the peritoneum was opened. The intestine was everywhere of a bluish tint. The mesentery had dark reddish blue areas in it chiefly at its connection with the small bowel. The involvement extended almost to the ileocecal valve. The vessels of the mesentery were thrombosed. Thirteen feet (396 cm.) of the small intestine were resected, and a lateral anastomosis with two rows of silk was done. The peritoneum and skin were closed in the usual manner.

The patient's general condition was fairly good after operation. Early the next morning his general condition became rapidly worse, and death occurred 19 hours after operation.

A necropsy was performed by Dr. H. A. Oberhelman who found extensive thrombosis of the superior mesenteric vein and its tributaries, mural thrombus of the aorta at the mouth of the superior mesenteric artery, and generalized serofibrinous hemorrhagic peritonitis.

A careful review of the literature was made of all the conditions that might cause gangrene or infarction of the small intestine and the present series was assembled. After collection of a number of cases of extensive resection, it was soon apparent that the mortality rate and the percentage of good results varied greatly with the different diagnoses. Thus, the results of extensive resection could not be given in a single statement any more than one could give the results of a similar number of laparotomies which included cholecystectomies, gastric resections, hysterectomies, and simple appendectomies. Then, too, certain intra-abdominal disorders required more extensive removal of small intestine than others so that again the results would not be comparable. For convenience in analyzing the results in this series, the following arbitrary classification of cases was made: The case was classified as a death if the patient died within 2 weeks of the operation, a poor result was obtained if death occurred within the first year after operation, and a fair result was considered if the patient had digestive or diarrheal disturbances after operation, or if death occurred later than 1 year as a consequence of the operation. Good results were considered as such only if the author stated there was a good result with no digestive or gastro-intestinal disturbances, or if the patient was able to return to work as before the resection. In referring to Table I, it can be seen that the greatest number of cases of resection over 200 centimeters occurred in 78 patients with volvulus of the small intestine or *Knotenbildung* of the sigmoid flexure and the small intestine. Incarcerated or strangulated hernia (45 cases), mesenteric thrombosis (34 cases), diseases of the female pelvic organs including uterine perforations with a curette (21 cases), and affections of the mesentery (19 cases) followed in order.

VOLVULUS AND KNOTENBILDUNG

The most common cause for extensive resection was volvulus. In this particular condition two entirely different situations must be recognized. Volvulus of the small intestine was the cause for resection in 27 cases (6, 15, 16, 38, 47, 54, 69, 73, 88—7 cases, 92, 93, 138, 140, 144, 157, 161—2 cases, 182, 187, 188, and 194), and although the average length was great (318 cm.) this class had a high percentage of good results (55.5 per cent). The second type of volvulus or *Knotenbildung* was described by Faltin in 1906 in which a knot formation involved the ileum and the sigmoid flexure. Forty-nine cases (41—11 cases, 47, 48, 88—32 cases, 113, 134, 162, and 187) were collected from the literature in which *Knotenbildung* of the sigmoid flexure and the small intestine required the removal of 200 centimeters or more of small bowel. Kallio has recently written a monograph on this subject, and he was able to assemble 161 examples of intestinal knot formation. Practically all of these cases have been reported in patients living in the region of the Baltic Sea. The highest mortality rate (65.3 per cent) for any particular cause necessitating massive resection of the small intestine occurred with *Knotenbildung* involving the sigmoid flexure and the ileum.

STRANGULATED HERNIA

The second most common cause for extensive resection was incarcerated or strangulated hernia. There were 26 examples (4, 7, 9, 11, 15, 49, 61—2 cases, 63, 65, 68, 79, 102, 103, 125, 133, 135, 143, 149, 158, 176, 185, 186, 191 and 192) of inguinal hernia, 6 (31, 36, 40, 62, 151, and 158) of femoral hernia, 6 (33, 57, 61, 76, 129, and 211) of umbilical, and 7 (15, 52, 80, 100, 104, 112, and 152) in which other types occurred or in which the type was not stated. The peculiar type of hernia *en W* occurred five times (79, 102, 103, 151, and 176) in this series, and the mortality was quite high (40 per cent). Pólya, in 1911, collected a group of 62 cases of hernia *en W* or retrograde incarceration in

TABLE I.—CONDITIONS REQUIRING MASSIVE RESECTION OF SMALL INTESTINE

Diagnosis	C	D	M%	R	GR	FR	PR	cm.	M	F	?
Volvulus and *Knotenbildung*	76	40	52.6	36	39.5	2.6		308	65	10	1
Sigmoid and ileum	49	32	65.3	17	30.5	4.0		300	45	4	
Small intestine	27	8	29.6	19	55.5			322	20	6	1
Strangulated hernia	45	11	23.9	32	32.6	10.9	17.7	291	23	15	7†
Inguinal	26	7	26.9	18	38.4	3.8	11.5	285	21	3	2*
Femoral	6	1	16.7	5		33.3	33.3	327	1	5	
Umbilical	6	3	50.0	3	16.7		16.7	289	0	5	1
Other types or type not known	7	0		6	28.6	28.6	14.3	299	1	2	4*
Mesenteric thrombosis	34	14	41.2	20	38.2	5.8		309	19	12	3
Female pelvic disease	21	4	19.0	17	38.0	9.5	19.0	415	0	21	
Uterine perforation	11	2	18.1	9	45.5	9.1	27.2	513	0	11	
Other pelvic disease	10	2	20.0	8	30.0	10.0	10.0	307	0	10	
Mesenteric tissues	19	4	21.0	14	26.3	21.0	5.2	331	13	3	3*
Primary mesenteric tumors	14	3	21.4	11	28.5	28.5		315	11	1	2
Mesenteric slits	3	1	33.3	2	33.3			449	2	1	
Other conditions	2	0		1			50.0	252	0	1	1*
Abdominal injuries	16	3	18.7	10	43.7		6.2	243	15	1	
War wounds	5	1	20.0	1				264	5	0	‡
Other conditions	11	2	18.2	9	63.7		9.1	233	10	1	
Tuberculosis of the intestine	16	2	12.5	14	37.5	25.0	18.7	245	7	8	1
Adhesions or bands	7	1	14.2	6	71.4			312	6	0	1
Miscellaneous	13	2	15.4	11	23.1	7.7	15.4	273	7	4	2
Cause not stated	10	5	50.0	5	30.0	10.0	20.0	284	1	1	8
Total	257	86	33.5	165	36.7	8.2	7.8	305	156	75	26

C—cases. D—deaths. M%—mortality percentage. R—recoveries. GR—percentage of good results. FR—percentage of fair results. PR—percentage of poor results. cm.—average length of resection in centimeters. M—male. F—female. ?—sex not stated. *—fate of 1 case unknown. †—fate of 2 cases unknown. ‡—fate of 3 cases unknown.

which there was a mortality of 41.9 per cent; thus, the results in the smaller series with resection compares favorably with the results of the disease entity.

MESENTERIC THROMBOSIS

Mesenteric thrombosis, as can be expected, contributed a fair number of cases (1, 2, 8, 18—3 cases, 21, 25, 58, 70, 72, 84, 86, 87, 94, 107, 110, 114, 115, 119, 120, 122, 132, 136, 146, 154, 167, 172, 179, 180, 205, 212, and author's cases Nos. 2 and 3) to the total. Elliott performed the first successful enterectomy for infarction due to mesenteric thrombosis when he resected 130 centimeters of small intestine in 1895. Jackson, Porter, and Quinby, in 1904, collected and reviewed 214 cases of mesenteric embolism and thrombosis. In their series there was only 1 (Greenough's case) massive resection of the small intestine. Forty-seven operations were performed with a mortality of 92 per cent. Trotter brought the total to 360 cases in 1913. Ackman estimated (1931) there were about 500 cases in the literature. Farah in 1929 collected 80 cases of enterectomy for mesenteric thrombosis with 42 recoveries; however, only a small percentage of these were extensive.

DISEASE OF THE FEMALE PELVIC ORGANS

Twenty cases of massive enterectomy (30, 32, 33, 50, 53, 56, 59—2 cases, 77, 108, 116, 127, 148, 155, 163, 168, 171, 207, 208, and 213) were necessary because of disease of the female pelvic organs. The most common cause in this group, of which there were 11 (56, 59—2 cases, 116, 127, 155, 163, 168, 171, 207, and 208), was perforation of the uterus with a curette. This usually occurred at the time of a criminal abortion. There was generally extensive injury to the mesentery associated with prolapse of great lengths of intestine. This class of cases required the removal

of the greatest length of small intestine, and the average length excised was far greater than for any other cause (513 cm.). In 3 cases, the almost unbelievable lengths of 820, 750, and 700 centimeters were excised and in each instance the patient recovered.

DISEASES OF THE MESENTERY

Derangements of the mesentery contributed 19 cases (12, 17, 35, 90, 91, 92, 98—2 cases, 105, 126, 130, 139, 150, 153, 169, 174, 190, 206, and 210) to the total. Tumors of the mesentery, either primary or secondary, comprised the greater percentage. This class of cases required a rather long excision of small intestine on an average (331 cm.), and the percentage of good results was not high (26.3 per cent). It is interesting to note there were 3 cases (35, 92, and 210) in which the small intestine became incarcerated in a slit in the mesentery.

ABDOMINAL INJURIES

Abdominal injuries accounted for a number of cases (13, 19, 64, 67, 82, 147, 165, 177, 193, 196, 199, 203—4 cases, and author's case No. 1). It must be agreed that the mortality rate of 18.7 per cent is ridiculously low. In comparison with the mortality in this series, the United States War Department reported 1,928 admissions for injuries to the abdomen and pelvis during the World War with 1,199 deaths or a mortality of 62.2 per cent. War wounds necessitated 5 massive resections, and these (13 and 203) are all reported from the British Army Medical Corps. In the official report of the War Department, the United States had 153, 537 admissions for battle injuries during the World War, and only 2 cases (excluding fatal cases) are recorded as "partial loss of the intestine."

TUBERCULOSIS OF THE SMALL INTESTINE

Tuberculosis contributed 16 cases to the total (6, 28, 29, 81, 97, 123, 128, 141, 175—7 cases, and 195). There were only 2 deaths, and the reported results were surprisingly good despite frequent statements in the literature that good results cannot be expected in tuberculous patients. Again it may be possible that poor results have not been reported.

MISCELLANEOUS CAUSES

Adhesions and bands accounted for 7 cases (10, 77, 89, 131, 157, 159, and 178), and there was a high percentage of good results (71.4 per cent). Miscellaneous causes constituted a total of 12 cases, and this included a variety of conditions: invagination of a polyp (36 and 170), intussusception of the small intestine (15 and 39), abdominal dehiscence (23), colloid carcinoma of the transverse colon with intestinal adhesions (55), gangrene of the ileum (59), intestinal obstruction (96), ileocecal tumor (111), gangrenous appendicitis and gangrenous ileum (142), knot of a free Meckel's diverticulum (157), ileus (160), and appendiceal abscess (201). The remainder (5, 15, 34, 70, 74, 75, 83, 95, 109, and 121) included 10 cases in which the cause for the resection was not stated.

TABLE II.—CORRELATION OF AGE AND THE RESULTS IN MASSIVE RESECTION

Age	C	D	M%	R	GR	FR	PR	?
1–10	2	0	00.0	2	100.0			
11–20	15	2	13.3	13	60.0	6.6	13.2	
21–30	57	14	24.5	43	38.6	10.5	8.7	
31–40	44	16	36.3	28	38.6	11.3	2.2	
41–50	38	17	45.8	21	31.6	10.5	10.5	
51–60	27	12	44.4	15	37.0	3.7	7.4	
61–70	22	7	31.8	14	31.8	9.0	4.5	1
71–up	9	6	66.7	3	11.1	11.1		
Not stated	43	12	27.6	26	18.6	2.3	2.3	5
Total	257	86	33.5	165	36.7	8.2	7.8	6

C—cases. D—deaths. M%—mortality percentage. R—recoveries. GR—percentage of good results. FR—percentage of fair results. PR—percentage of poor results. ?—fate unknown.

AGE

The age was found to vary widely in the 214 instances in which it was mentioned (Table II). The extremes ranged from 8 to 76. Ruggi's resection of 330 centimeters in a boy of 8 and Blayney's report of a resection of 253 centimeters in a boy of 10 are cases of the two youngest patients on record. At the other extreme there were 9 patients over 70 years of age. Pólya and Heller each reported a case in patients of 76 years. In passing, it may be noted that Flint successfully resected 100 centimeters of ileum from a male infant of 11 months for gangrene due to an intussusception. Jackson's case of successful resection of 142 centimeters of gangrenous small intestine for herniation through a mesenteric defect has already been mentioned. In consulting the table, it is seen that the greatest number of resections occurred between the ages of 21 and 30, and the next in order was 31 to 40. There was considerable increase in the mortality of the operation above the age of 30 as compared to the results between the ages of 11 and 30. Flint found experimentally that young animals did not withstand resection as well as older dogs. In this clinical series, better results have been recorded under the age of 20, and there

TABLE III.—CORRELATION OF THE SEX AND THE RESULTS IN MASSIVE RESECTION

Sex	C	%	D	M%	R	GR	FR	PR	?
Male	156	61.1	66	42.8	86	35.9	5.1	2.5	4
Female	75	28.8	14	18.8	61	35.0	12.1	13.5	
Not stated	26	10.1	6	23.0	18	19.2	7.7	3.8	2
Total	257	100.0	86	33.5	165	36.7	8.2	7.8	6

C—cases. %—percentage of total cases. D—deaths. M%—mortality percentage. R—recoveries. GR—percentage of good results. FR—percentage of fair results. PR—percentage of poor results. ?—fate not stated.

is comparatively little difference in the good results obtained between the ages of 21 and 70.

SEX

The sex was stated in 231 of the 257 cases, and in analyzing the sex incidence nothing of importance was revealed (Table III). There were 156 males and 75 females. The higher mortality in males (42.8 per cent) as compared to that of females (18.8 per cent) can be explained by the higher mortality of mesenteric thrombosis, and volvulus between the ileum and sigmoid flexure in which males predominate. The percentage of good results in the sexes was relatively the same, but the percentage of poor results in females was much more frequent.

LENGTH OF RESECTIONS

A correlation was made between the amount of intestine removed and the results (Table IV). As can be expected, the greatest number of cases (143) measured between 200 and 299 centimeters, the number diminishing as the length increased. The mortality rate was comparable in any length from 200 to 499 centimeters. In general, it must be admitted that as the amount of intestine removed became longer the results became poorer.

OPERATIVE PROCEDURES

A correlation was also made between the type of anastomosis and the results (Table V). The best results, as far as operative mortality was concerned, followed lateral anastomosis of the small intestine (20.6 per cent), and lateral anastomosis of the small intestine with the ascending colon (18.7 per cent), whereas lateral anastomosis with a Murphy button showed the poorest figures (60.0 per cent). Cases in which an anus præternaturalis was made had a high mortality rate (64.7 per cent), but it must be remembered that many of these cases were in desperate circumstances at operation, and this procedure was used in an endeavor to conserve time.

TABLE IV.—CORRELATION OF THE AMOUNT RESECTED AND THE RESULTS IN MASSIVE RESECTION

Length resected	C	D	M%	R	GR	FR	PR	?
200–299	143	51	35.9	86	30.8	6.3	6.3	6
300–399	76	27	35.5	49	32.9	9.2	7.9	
400–499	21	5	23.8	16	57.1		4.8	
500–599	13	2	15.4	11	53.8	15.4	7.7	
600–699	1	1	100.0	0				
700–799	2	0		2			100.0	
800–up	1	0		1		100.0		
Total	257	86	33.5	165	36.7	8.2	7.8	

C—cases. D—deaths. M%—mortality percentage. R—recoveries. GR—percentage of good results. FR—percentage of fair results. PR—percentage of poor results. ?—fate unknown.

METABOLIC STUDIES

Of the series of collected cases, 35 had some sort of quantitative metabolic determinations of the nitrogen, carbohydrate, or fat of the stool (3, 6, 25, 36, 39, 69, 123, 131, 132, 140, 141, 156, 159, 165, 171, 172, 175—7 cases, 178, 183, 185, 186, 187, 190, 195, 201, 205, 212, 213 and author's case No. 1). In all cases in which over 380 centimeters of small intestine were resected there was a definitely abnormal loss of nitrogen in the stool. Excessive fat in the stool was seen in some cases in which as little as 225 centimeters (Miyake's case) were excised. Very few determinations have been made of both the urinary and fecal nitrogen in an attempt to study the nitrogen balance of the patient.

Studies were made of the blood and nitrogen balance in the author's first case by Dr. L. R. Dragstedt. This is the only case in the entire collected series in which any chloride studies were made, and in this instance it is enlightening to know the patient was able to maintain his chloride balance adequately despite only 55 centimeters of small intestine interposed between the stomach and the middle of the transverse colon. In addition to the routine laboratory work, the following determinations were made: Blood hydrogen-ion concentration, 7.44; carbon dioxide combining power, 66.45 volumes per cent; blood chlorides (expressed as Cl), 307.4; total base, 148.8, and non-protein nitrogen 26.7 milligrams per cent. On December 30, the plasma protein was 4.094 grams per 100 cubic centimeters of plasma and by February 2, 1931, this had fallen to 3.48 grams. Nitrogen balance studies were made in three determinations of 3 days each for 9 consecutive days. The protein lost by stool was

TABLE V.—CORRELATION OF THE TYPE OF ANASTOMOSIS AND THE RESULTS IN MASSIVE RESECTION

Type of anastomosis	C	D	M%	R	GR	FR	PR	?
Lateral anastomosis	78	22	28.2	54	44.8	8.9	5.1	
Small intestine (suture)	34	7	20.6	25	55.8	8.8	2.9	2
Small intestine (button)	5	3	60.0	2	20.0		20.0	
Small intestine with ascending colon (suture)	16	3	18.7	13	62.5	12.5		
Small intestine with ascending colon (button)	3	1	33.3	2	66.7			
Small intestine with transverse colon	17	8	47.0	9	17.6	11.8	11.8	
Small intestine with colon	3	0		3	66.7	33.3		
End-to-end anastomosis	72	26	36.6	46	47.2	4.1	2.7	
End to end (suture)	53	19	36.5	33	45.3	3.7	1.8	
End to end (button)	19	7	36.8	12	52.6	5.2	5.2	
End-to-side anastomosis	12	3	25.0	9	33.3	33.3		
Small intestine with ascending colon	5	2	40.0	3	20.0	40.0		
Small intestine with transverse colon	2	1	50.0	1	50.0			
Small intestine with colon	1	0		1	100.0			
Undesignated components	4	0		4	25.0	50.0		
Mixter tube in upper portion	1	1	100.0	0				
Anus præternaturalis	17	11	64.7	5	23.5		5.5	1
Type not stated	77	23	29.4	51	15.4	7.7	15.4	3
Total	257	86	33.5	165	36.7	8.2	7.8	

C—cases. D—deaths. M%—mortality percentage. R—recoveries. GR—percentage of good results. FR—percentage of fair results. FR—percentage of poor results. ?—fate unknown.

found to be 33.9 per cent, 36.0 per cent, and 41.6 per cent in each period (Table VI). These figures might be criticized in view of the work of Mattill and Hawk who showed that bacterial nitrogen constitutes 53.9 per cent of the total fecal nitrogen in normal subjects, but on the other hand it is logical to assume that the bacterial nitrogen would be markedly reduced in a patient with severe diarrhea in which the head of a barium column reached the rectum approximately 4 hours after ingestion.

PERIOD OF SURVIVAL

A survey of the cases in the series was made with reference to the period of survival after operation, and the table (Table VII) gives a résumé of end-results in the reported cases. Kallio made a conscientious effort to follow the cases in his article, and a great number of the long survivals are reported in his collection. Two cases have survived 18 years after operation; these are Kallio's case in which patient was operated on by Ignatius who removed 300 centimeters of small intestine and 50 centimeters of ascending colon were resected, and Elfving's case in which patient was operated on by Runeberg who removed 325 centimeters of small intestine. In Zusch's case, Barth operated and resected 316 centimeters of small intestine. This patient was reported alive 14 years after operation. Matthaei's case, in which 530 centimeters of small intestine were excised, died of bronchopneumonia after being in good health for 11 years after operation. The only other reported case with a 10 year survival was the case operated on by Rupp and reported by Frangenheim in which 400 centimeters of small intestine had been removed.

DIARRHEA

Diarrhea is the most common and the most disturbing postoperative complication, both clinically and experimentally, and this symptom may be so severe as to cause the death of the patient. Diarrhea caused by extensive resection cannot be controlled by drugs, and the only hope lies in dietary management. Experience and laboratory experiments have borne out the fact that patients can be expected to fare much better on a fat poor, protein adequate, and carbohydrate rich diet.

EXPERIMENTAL STUDIES

Senn was perhaps the first individual to do experimental work on resection of the small intes-

TABLE VI.—NITROGEN BALANCE STUDIES IN CASE 1

Date	Weight	Food ingested			Calories	Urine N. Grains	Fecal N. Grains	Protein Equivalent	Protein Loss, %
		C	P	F					
1– 9–31	52.6 Kg.	292	50	52	1836	4.46			
1–10–31	53.2	274	51	55	1795	5.31			
1–11–31	53.0	226	42	46	1486	4.39	7.77	48.56	33.9
1–12–31	52.6	183	48	57	1437	4.02			
1–13–31	52.7	294	39	38	1614	4.85			
1–14–31	52.8	247	44	47	1587	5.26	7.55	47.18	36.0
1–15–31	52.5	236	45	47	1547	6.50			
1–16–31	52.8	296	50	54	1774	5.56			
1–17–31	53.0	201	37	37	1285	5.63	8.64	55.0	41.6

tine. In 1888, he performed enterectomies on 4 dogs and 3 cats and, from these 7 experiments, he concluded that excision of more than one-third of the length of the small intestine was dangerous to life. Monari, after a series of resections on dogs in 1896, believed that seven-eighths of the small intestine could be removed with safety. Erlanger and Hewlett studied the problem in 1901, and they decided that dogs with 70 to 83 per cent of the combined jejunum and ileum removed may live indefinitely after recovery from the operation. In 1907, Evans and Brenizer performed resections on dogs, and from their experiments they concluded that dogs would survive 50 per cent removal of the small intestine almost invariably, and that they would tolerate 67 per cent removal with the best of care. They stated that there was no hypertrophy of the remaining intestine in the most extensive enterectomies. Flint believed that dogs could withstand a resection of 50 per cent of their small intestine and return to normal, but that the animals did not return to normal even though they survived the operative removal of 75 per cent of the small intestine. He also contended that there was a hypertrophy and hyperplasia of the remaining small intestine, and he termed this change a compensation. Wildegans reported on a number of experiments in 1925. He found that proteins and fats were not well digested in the first 4 weeks after resection of two-thirds of the small intestine in dogs, but that the animals regained this ability to a certain extent later. He found that dogs died from inanition when 70 to 80 per cent of the small intestine was removed. Kunz and Molitor also came to the conclusion that 70 per cent represented the limits of small intestinal resection in dogs.

TABLE VII.—PERIOD OF SURVIVAL AFTER MASSIVE RESECTION OF THE SMALL INTESTINE

Time	Cases reporting	Deaths	Good	Fair	Poor results
1 to 3 months	23	7*	14	2	7
3 to 6 months	17	2	11	4	2
6 to 12 months	26	7*	14	6	6
1 year	15	2	11	2	2
2 years	11	5†	7	2	
3 years	10	1*	6	3	1
4 years	3	0	2		1
5 years	1	0	1		
6 years	2	0	2		
7 years	2	0	2		
8 years	1	0	0	1	
10 years	1	0	1		
11 years	1	1*	1		
14 years	1	0		1	
18 years	2	0	2		

*1 case died of causes not referable to the resection.
†2 cases died of causes not referable to the resection.

CONCLUSION

In the collection of 257 cases of extensive enterectomy, it is obvious that the surgeon is dealing with patients who are desperately ill. It is logical to conclude that the mortality rate of 33.5 per cent does not represent the true operative mortality of this spectacular procedure because of the tendency to report only the successful cases. Good results after survival of the operation depend on the condition and length of the small intestine remaining, on the disease condition necessitating the massive resection, and on the feeding of a diet poor in fat, adequate in protein, and rich in easily assimilable carbohydrates. From a study

of the total series the postoperative results were reviewed in an attempt to answer the question, "How much of the small intestine can be removed and still allow the patient to live and return to normal health?" The prepared tables do not give a direct answer to this query so that another approach to the problem was made. It was found that a total of 86 cases with subsequent good results had an average resection of 310 centimeters; this constituted an average of 47.2 per cent of the total small intestinal length (657 cm.) found in a study of 1,161 cases. In 21 cases classified as fair results, an average resection of 367 centimeters, or 55.8 per cent of the total length of small intestine, had been done. Fifteen cases with poor results had an average resection of 348 centimeters, or 52.9 per cent of the average total small intestinal length. A conservative estimate as to the limits of small intestinal resection from the foregoing analyses would be as follows: Discounting the dangers of the operation itself and its concomitant possible complications, a patient can withstand a massive resection of 33 per cent of the length of the small intestine and expect the digestive tract to return to normal function; 50 per cent removal constitutes the upper limit of safety in extensive enterectomy; and resections above 50 per cent must necessarily obtain poorer results even though an exceptional case may be better than predicted.

SUMMARY

1. Three cases of massive resection of the small intestine are reported.

2. A total of 257 cases of massive resection of the small intestine was collected from a review of the literature, and an analysis of the collected series was made.

The author wishes to express his appreciation to Dr. D. B. Phemister, Dr. L. R. Dragstedt, and Dr. W. T. Harsha for the privilege of reporting their cases.

BIBLIOGRAPHY

1. Ackman, F. D. Occlusion of the mesenteric arteries with the report of five cases. Canadian M. Ass. J., 1931, 25: 657–663.
2. Addison, Oswald L. A case of thrombosis of a considerable portion of the superior mesenteric vessels without any discoverable cause. Brit. J. Surg., 5: 173–174.
3. Albu, A. Ueber die Grenzen der Zulaessigkeit ausgedehnter Darmresectionen. Berl. klin. Wchnschr., 1901, 38: 1248–1252.
4. Allen, E. S. Report of cases of intestinal resection. Kentucky M. J., 1923, 21: 267–274.
5. Amour. Quoted by Ghedini from Nigrisoli's series, loc. cit.
6. Axhausen, G. Ueber die obere Grenze fuer die Zulaessigkeit ausgedehnter Duenndarmresektionen. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1909, 21: 55–66; also Deutsche med. Wchnschr., 1909, p. 145.
7. Bäcker, Istvan. Ausgedehnte Darmresektion. Orvosi hetil., 1931, 1: 312–313.
8. Banke, Kai. Ein Fall von Mesenterialgefassverstopfung mit Resektion von 435 cm. Duenndarm. Hosp.-Tid., 1932, pp. 445–452. Abstracted in Zentralorgan f. d. ges. Chir., 1932, 58: 709.
9. Baracz, Roman von. Brucheinklemmung, complicirt durch Thrombose der Vena mesenterica superior. Arch. f. klin. Chir., 1907, 83: 478.
10. Bastianelli. Quoted by Ghedini from Nigrisoli's series, loc. cit.
11. Bedarida, Nino V. Occlusioni intestinali a duplice sede. Arch. ital. di Chir., 1928, 22: 634–644.
12. Bell, George, and Inglis, K. A case of sarcoma of mesentery; successful removal involving resection of ascending colon and 237.5 cm. of ileum with pathological report. M. J. Australia, 1923, 1: 375.
13. Bell, Gordon. Resection of the small intestine for war wounds. J. Roy. Army Med. Corps, 1921, 36: 351–360.
14. Beneke. Ueber die Laenge des Darmkanals bei Kindern, sowie ueber die Capacitaet des Magens Neugeborener. Deutsche med. Wchnschr., 1880, pp. 448–449.
15. Bergmann. Quoted by Ghedini from Nigrisoli's series, loc. cit.
16. Berkofsky, K. Erfahrungen bei der operativen Behandlung des abgeklemmten brandigen Darmes. Deutsche Ztschr. f. Chir., 1911, 109: 133–159.
17. Bernays, Augustus C. Sarcoma of the mesentery; resection of 119 inches of small intestine; recovery. Ann. Surg., 1902, 35: 790–801, 835.
18. Blackburn, J. H. Mesenteric thrombosis and embolism; report of 36 cases. South. M. J., 1916, 9: 810–819.
19. Blayney, Alexander. On the removal of great lengths of intestine. Brit. M. J., 1901, 2: 1456–1458.
20. Boeckel, Jules. Resection de deux mètres d'intestin (ileon, caecum, et colon ascendant) dans une forme d'appendicite non encore décrite. Bull. Acad. de méd., Par., 1912, 68: 241–245.
21. Bonnot, Edmond. Mesenteric thrombosis with 88 inches of intestine resected. Med. Rec., 1918, 93: 502.
22. Bornstein, Fritz. Ueber morphologische Veraenderungen nach ausgedehnter Duenndarmresektion. Arch. f. path. Anat., 1933, 291: 921–936. See also Matthaei, loc. cit.
23. Brenizer, A. G. Extensive resections of small intestines. Ann. Surg., 1929, 89: 675–681.
24. Brohee. Extensive resection of small intestine; anastomosis of stomach and lower ileum. Bruxelles méd., 1929, 9: 685–687. Abstracted by W. F. Prior & Co., Inc.
25. Brougham, E. J. A case of resection of 11½ feet of small intestine. Surg., Gynec. & Obst., 1907, 4: 782.
26. Bruett. Embolie und Thrombose der arteria mesenterica superior. Zentralbl. f. Chir., 1922, 49: 611. See Schumm and Papendieck, loc. cit.
27. Bryant, J. Observations upon the growth and length of the human intestine. Am. J. M. Sc., 1924, 167: 499–520.
28. Caird. Quoted by Ghedini from Nigrisoli's series, loc. cit.
29. Cannaday, John E. Long resections of the intestine. Ann. Surg., 1919, 69: 425–431.

30. CARTOLARI, ENRICO. Resezione di due metri e trenta centimetri di intestino tenue ed isterectomia addominale per lesioni traumatiche di origine ostetrica. Guarigione. Gazz. d. osp., 1919, 40: 386–388.
31. CHILDE, CHARLES P. A case of successful resection of nine and one half feet of small intestine for gangrene. Brit. M. J., 1907, 2: 891–892.
32. CROSSEN, H. S. Case of hernia through a rupture of the uterus necessitating resection of 13 feet of intestine. Am. J. Gynec. & Obst., 1898, 12: 45–51.
33. CZERNY. Quoted by Ghedini from Nigrisoli's series, loc. cit.
34. DEKONSKI. Reference by Istomin. Russ. med. Rundschau., 1910, 8: 329. Cited by Soyesima, loc. cit.
35. DELKESKAMP. Ueber ausgedehnte Duenndarmresektionen. Beitr. z. klin. Chir., 1919, 115: 176–180.
36. DENK, WOLFGANG. Ausgedehnte Darmresektion mit Ausgang in Heilung. Wien. klin. Wchnschr., 1907, 20: 1649–1652.
37. Idem. Ueber die Prognose ausgedehnter Duenndarmresektionen. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1910, 22: 146–153.
38. DOERFLER, HEINRICH. Kann der Mensch ohne Duenndarm leben? Kasuistischen Beitrag. Zentralbl. f. Chir., 1923, 50: 1502–1504.
39. DOROW, A. R. E. Ausgedehnte Duenndarmresektion und Ausnutzung der Nabrungsstoffe. Dissertation, Hamburg, 1932.
40. DREESMANN. Ueber groessere Darmresectionen. Berl. klin. Wchnschr., 1899, 36: 337–339.
41. ELFVING, A. R. Kasuistiska bidrag till kännedomen om knutbilding mellan tunntarm och flexura sigmoidea. Finska läk-sällsk. handl., 1924, 66: 602–626. Abstracted in Internat. Abst. Surg., 1925, 41: 21.
42. Idem. Kasuistische Beitraege zur Kenntnis der Knotenbildung zwischen Duenndarm und Flexura sigmoidea. Acta chir. scand., 1925, 59: 185–207.
43. ELLIOTT. Operative relief of gangrene of the intestine due to occlusion of the mesenteric vessels. Ann. Surg., 1895, 21: 9–23.
44. ENOCHIN. Reference by Istomin. Russ. med. Rundschau., 1910, 8: 329. Cited by Soyesima, loc. cit.
45. ERLANGER, JOSEPH, and HEWLETT, ALBION W. A study of the metabolism in dogs with shortened small intestines. Am. J. Physiol., 1901, 6: 1–30.
46. EVANS, HERBERT M., and BRENIZER, A. G. Resection of the small intestine in the dog. Johns Hopkins Hosp. Bull., 1907, 18: 477–480.
47. FALTIN, R. Kasuistische Beitraege zur Kenntnis der Knotenbildung des Darms. Deutsche Ztschr. f. Chir., 1906, 84: 477–487.
48. Idem. Bidrag till kännedomen om tarmknutar. Finska Läk-sällsk. handl., 1909, 51: 326–356.
49. FANTINO. Contributo allo studio delle estese resezioni intestinali. Gazz. med. di Torino, 1896, 47: 181. Abstracted in Centralbl. f. Chir., 1896, 23: 614.
50. Idem. Neuovo contributo allo studio delle estese resezioni intestinali. Riforma med., 1902, 4: 62–64. Abstracted in Jahresb. f. Chir., 1902, 8: 755.
51. FARAH, JEAN. L'infarctus hémorrhagique de l'intestin. Thèse de doct., Paris, 1929.
52. FISCHER, A. Geheilter Fall von ausgedehnter Darmresektion. Centralbl. f. d. Grenzgeb. d. Med. u. Chir., 1906, 9: 70. Quoted from Flechtenmacher, loc. cit.
53. FLATER and SCHWERINER. Ueber die Prognose ausgedehnter Duenndarmresektionen. Berl. klin. Wchnschr., 1920, 57: 749–752.
54. FLECHTENMACHER, CARL. Ueber ausgedehnte Duenndarmresektionen. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1917, 29: 451–468.
55. FLINT, J. M. The effect of extensive resections of small intestine. Johns Hopkins Hosp. Bull., 1912, 23: 127–144.
56. FLOSDORF, P. Bericht ueber einen Fall grosser Duenndarmresektion. Zentralbl. f. Chir., 1925, pp. 1597–1598.
57. FOSS, H. L. Intestinal resection in cases of massive umbilical hernia. Surg., Gynec. & Obst., 1923, 36: 263–270.
58. FOWLER, O. S. Discussion of superior mesenteric thrombosis. Southwestern Med., 1928, 12: 549–555. See Wilburn Smith, loc. cit.
59. FRANGENHEIM. Spaetfolgen nach ausgedehnter Duenndarmresektion. Arch. f. klin. Chir., 1925, 138: 146–150.
60. FRANKAU, CLAUDE. Strangulated hernia: a review of 1487 cases. Brit. J. Surg., 1931, 19: 176–191.
61. FRANZ. Herniologische Beobachtungen mit besonderer Berueecksichtigung der Radicaloperationen. Deutsche Ztschr. f. Chir., 1899, 51: 1–120.
62. FRIEDRICH, P. L. Ueber den Nutzen der funktionellen Ausschaltung grosser Darmabschnitte bei septischer Peritonitis. Med. Klin., 1905, 1: 25–26. See also Denk, loc. cit. (37).
63. FRIELE, J. Ventrikel und Darm chirurgie aus der Privatklinik Bergens in den 4 Jahren 1894–1898. Medicinsk Rev. Abstracted in Jahresb. f. Chir., 1898, 4: 634.
64. GARNER, E. L., and BISSETT, G. W. Extensive resection of small bowel following trauma in which 261 cm. were removed with recovery. Canadian M. Ass., J., 1931, 25: 320–322.
65. GHEDINI, ANNIBALE. Estese resezioni ed esclusioni dell' intestino. Clin. chir., 1905, 13: 1217–1243. Abstracted by W. F. Prior & Co. Inc.
66. GIBSON, CHARLES LANGDON. A study of 1000 operations for acute intestinal obstruction and gangrenous hernia. Ann. Surg., 1900, 32: 486–514; 676–707.
67. GIORDANO, F. P., and TURZI, G. DI. Reseccion intestinal amplia por grave traumatismo abdominal. Semana méd., 1931, 38: 273–275.
68. GOBIET, JOSEPH. Ueber Versehluss der Mesenterialgefaesse nebst Mitteilung eines operativ geheilten Falles. Wien. klin. Wchnschr., 1911, 24: 1552–1562.
69. GOEBELL, RUDOLF. Erfolgreiche Resektion von 3 m. Ileum wegen Volvulus und inner Einklemmung. Deutsche Ztschr. f. Chir., 1905, 77: 608–612.
70. GORDON-TAYLOR, G. Discussion on the diagnosis and treatment of injuries of the intestines. Brit. M. J., 1921, 2: 639–643.
71. GREENOUGH, R. B. See Jackson et al, loc. cit.
72. GREENSFELDER, LOUIS A. Thrombosis of the superior mesenteric artery. Ann. Surg., 1905, 41: 302–303.
73. GUIBAL, J. Quatre cas de volvulus du grèle. Bull. et mém. Soc. nat. de chir., 1929, 55: 1417–1422. Abstracted in Internat. Abst. Surg., 1930, 51: 30–31.
74. HAGGARD, W. D. Personal communication to Cannaday.
75. HAHN. Quoted by Ghedini from Nigrisoli's series, loc. cit.

76. HAHN, EUGEN. Ueber einige Erfahrungen auf dem Gebiete der Magendarm chirurgie. Deutsche med. Wchnschr., 1897, 23: 650–653.
77. HARRIS, GEORGE R. Resection of nearly 8 feet of gangrenous intestine; recovery. Med. Rec., 1902, 62: 563–566.
78. HAYES. Quoted by Harris, loc. cit.
79. HELLER, E. Zur Kenntnis der retrograden Darminkarzeration. Med. Klin., 1908, 4: 151–155.
80. HOFMANN, M. Ueber ausgedehnte Darmresektionen. Arch. f. klin. Chir., 1924, 131: 251–268.
81. HOFMEISTER. Quoted by Ghedini from Nigrisoli's series, loc. cit.
82. ISELIN. Peritonisierung des Mesenterialstumpfes mit freiem Netz bei ausgedehnter Darmresektion. Zentralbl. f. Chir., 1912, 39: 739–740.
83. ISTOMIN. Russ. med. Rundschau., 1910, 8: 329. Quoted from Soyesima, loc. cit.
84. JACKSON, J. M., PORTER, C. A., and QUINBY, W. C. Mesenteric embolism and thrombosis. J. Am. M. Ass., 42: 1469–1475; 43: 25–29, 110–114, 183–187.
85. JACKSON, R. H. Extensive resection of small intestine in an infant. Surg., Gynec. & Obst., 1925, 40: 55–61.
86. JERAULD, E. N. C., and WASHBURN, W. W. Extensive resection of small intestine; removal of 19 feet of ileum and jejunum. J. Am. M. Ass., 1929, 92: 1827–1830.
87. JUDIN, S. Ein operativ geheilter Fall akuter Thrombose der Mesenterialgefaesse. Novyj. chirurg. Arch., 1926, 11: 140–145. Abstracted in Zentralbl. f. d. ges. Chir., 1927, 39: 295–296.
88. KALLIO, K. E. Die Knotenbildungen des Darmes. Acta chirurg. scand., 1932, 70: Suppl. 21, 1–278.
89. KARLOV, A. Bukbrack efter appendicitoperation. Hygiea, 1903, 65: 460–471.
90. KARSTROEM, W. Fibromyoma retroperitoneale Laparotomie Resektion des Duenndarms (2.20 m.). Extirpation des Tumors. Heilung. Hygiea, 1902, p. 472. Abstracted in Jahresbr. f. Chir., 1902, 8: 657.
91. KENGLA, LOUIS A. Fibroma of mesentery. Occidental M. Times, 1902, 16: 140–141.
92. KIMBAROVSKIJ, M. Zur Frage ausgedehnter Resektionen des Duenndarms. Novyj. chirurg. Arch., 1931, 22: 551–555. Abstracted in Zentralorgan f. d. ges. Chir., 1931–1932, 56: 815.
93. KIRKWOOD, W. L. Torsion of the small intestine; resection of 8 feet of intestine; recurrence of torsion. Med. J. Australia, 1915, 2: 49–50.
94. KOCHER. Quoted by Ghedini from Nigrisoli's series, loc. cit.
95. KOCHER, TH. Textbook of Operative Surgery. 3d Eng. edit., pp. 625–626. A. & C. Black, 1911.
96. KOEBERLE. Résection de deux metres d'intestin grele. Guérison. Bull. de Acad. de méd., 1881, 8: 249–250.
97. KOPFSTEIN. W. Beitrag zu ausgedehnten Darmresektionen. Wien. med. Bl., 1910, 33: 16.
98. KUKULA. Ueber ausgedehnte Darmresectionen. Arch. f. klin. Chir., 1900, 60: 887–950.
99. KUNZ, HUBERT, and MOLITOR, HANS. Ueber die Ursachens der Ernaehrungsstoerungen nach ausgedehnten Duenndarmresektionen und ihre Behandlung. Arch. f. exper. Path. u. Pharmakol., 1928, 132: 50–62. Abstracted in Zentralorgan f. d. ges. Chir., 1928, 44: 463.
100. KUSCHEWA, M. N., and MALINOWSKY, N. N. Eine Operation der Hernia duodenojejunalis incarcerata mit ausgedehnter Resektion des Duenndarms. Zentralbl. f. Chir., 1927, 54: 525–528; Zentralorgan f. d. ges. Chir., 1927, 38: 315.
101. LAMB. Quoted by Bryant, loc. cit.
102. LANGER, ARMEN. Ueber retrograde Inkarzeration des Darms. Wien. klin. Wchnschr., 1903, 16: 475–478.
103. LAUENSTEIN, CARL. Ist es moeglich "Darmsclingen im eingeklemmten Bruch" zu diagnostizieren? Zugleich ein neuer Beitrag zu der Pathologie der "Hernie en W" resp. der "retrograden Darminkarzeration." Deutsche Ztschr. f. Chir., 1909, 100: 155–180.
104. LAUWERS. Des résections étendues de l'intestin grèle. J. de chir. et ann. belge de chir., 1901, 1: 739–752.
105. LEXER, E. Operation eines Mesenterialfibromes mit ausgedehnter Resection des Duenndarmes. Berl. klin. Wchnschr., 1900, 37: 4–5. See also Albu, loc. cit.
106. LIEBLEIN, VIKTOR. Einige Bemerkungen zur Frage der Prognose der ausgedehnten Duenndarmsresektionen. Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1911, 23: 1–12.
107. LINDNER, H. Ueber Thrombose der Mesenterialgefaesse. Berl. klin. Wchnschr., 1905, 42: Fest-Num., 5–7.
108. LITTLEFIELD, JOHN R. Resection of 13 feet of ileum. J. Am. M. Ass., 1919, 73: 835–836.
109. LONG, J. W. Personal communication to Cannaday.
110. LOOP, R. G. Mesenteric vascular occlusion with report of 9 cases in which operation was performed. J. Am. M. Ass., 1921, 77: 369–373.
111. LORENZ, H. Eine der ausgedehntesten Darmresektion die bisher an Lebenden ausgefuehrt wurden. Wien. klin. Wchnschr., 1906, 19: 610–611.
112. LUKESOVA. Incarcerierte gangränoese Hernien im Deutschbroder Krankenhause, 1898–1920. Časop. lék. česk., 60: 480–483. Abstracted in Zentralorgan f. d. ges. Chir., 1921, 14: 424.
113. LUNDBERG, SVEN. Ein Fall an ausgedehnter Duenndarmresektion. Acta chirurg. Scand., 1920, 52: 413–435.
114. MCGUIRE, EDGAR R. Successful removal of over 11 feet of small intestine. Surg., Gynec. & Obst., 1913, 16: 40–42.
115. MCGUIRE, STUART. Mesenteric thrombosis with report of two cases. Virginia M. Month., 1923, 50: 23–26.
116. MATTHAEI, F. Ueber ausgedehnte Duenndarmresektion und ihre Folgen. Arch. f. path. Anat., 1925, 254: 345–353. See also Fiedler. Zentralbl. f. Gynaek., 1923, 47: 180, and Bornstein, loc. cit.
117. MATTILL, H. A., and HAWK, P. B. A method for the quantitative determination of fecal bacteria. J. Exper. Med., 1911, 14: 433–444.
118. MAYDL. Quoted from Kukula's series and by Ghedini, loc. cit.
119. MEYER, JOSEPH L. Mesenteric vascular occlusion. Ann. Surg., 1931, 94: 88–96.
120. MICHAEL, P. R. Thrombosis venae mesentericae. Nederl. Tijdschr. v. Geneesk., 1925, 69: 584–588 Abstracted in Zentralorgan f. d. ges. Chir., 1926, 36: 410.
121. MITCHELL, A. B. Discussion. Med. Rec., 1909, 76: 330.
122. MITCHELL, J. F. Mesenteric thrombosis. Ann. Surg., 1923, 77: 299–305; Tr. South. Surg. Ass., 1923, 35: 223–240.
123. MIYAKE, H. Ueber ausgedehnte Darmresektion mit einer kurzen Bemerkung ueber die normale Laenge des Jejuno-Ileum bei dem Lebenden. Arch. f. klin. Chir., 1910, 93: 768–783.

124. MONARI, UMBERTO. Experimentelle Untersuchungen ueber die Abtragung des Magens und des Dunndarms beim Hunde. Beitr. z. klin. Chir., 1896, 16: 479–492.
125. MONPROFIT, M. Résection de 3 mètres 10 centimètres d'intestin dans une cure radicale de hernie volumineuse. Rev. de Chir., 1899, 20: 579–580.
126. MORTON, H. R. Kelly-Noble Abdominal Surgery, p. 442. Philadelphia, 1908.
127. MUELLER, A. Zur Kasuistik der Uterus perforation mit Darmverletzung. Zentralbl. f. Gynaek., 1917, 41: 311–315.
128. NESTOR, V. Personal communication; nine occlusions of the small intestine caused by cicatricial stenosis; chronic appendicitis; cyst of right ovary; convalescence after resection of 2.26 m. of small intestine. Spitalul, Bucharest, 1931, 51: 9–11. Abstracted by W. F. Prior & Co. Inc.
129. NICOLI. Quoted from Flechtenmacher and also from Moynihan's Abdominal Operations. 4th ed., 1: 543–547. Philadelphia: W. B. Saunders Co., 1926.
130. NICOLL, JAMES H. Demonstration at Medico-chirurgical Society of Glasgow, January 19, 1912. Glasgow M. J., 1912, 77: 447.
131. NIGRISOLI, B. Sulle resezioni estese dell'intestino. Soc. ital. di chir., 1902. Abstracted in Jahresb. f. Chir., 1902, 8: 754. See also Vitali, Jahresb. f. Chir., 8: 757, and Flechtenmacher, loc. cit.
132. NIKITIN, A. Ein Fall der Resektion von 594 cm. Duenndarm infolge einer akuten Thrombose der V. mesenterica sup. Novyj. chirurg. arch., 1929, 19: 54. Abstracted, Internat. Abst. Surg., 1930, 51: 31.
133. NOLAND, LLOYD, and WATSON, FRED C. Embolism and thrombosis of the superior mesenteric artery. A report of one case. Ann. Surg., 1913, 58: 459–465.
134. NYSTRÖM, G. Till dännedomen om tarmknutar. Finska läk-sällsk. handl., 1914, 56: 449–462.
135. OBALINSKI, ALFRED. Ueber Laparotomie bei innernem Darmverschluss auf Grund eigener 110 Faelle. Arch. f. klin. Chir., 1894, 48: 1–53.
136. OLIVECRONA, HERBERT. A case of embolism of the superior mesenteric artery. Acta chirurg. scand., 1924, 57: 403–410. Sjövall, loc. cit.
137. ONODERA and JANO. Quoted by Soyesima, loc. cit.
138. ORGEL, D. H. Thrombosis of the superior mesenteric vessels and volvulus of the small intestine; resection and recovery. New York M. J., 1923, 117: 695.
139. PAITRE and CARRIVE. Conséquences physio-pathologiques d'une résection de 2 m 50 cm. d'intestine grèle. Lyon chir., 1923, 20: 610–614.
140. PALMEN, A. J. Fall von Darmknoten, ausgedehnte Duenndarmresection, Nachpruefung der Verdauungstaetigkeit. Acta chirurg. Scand., 1925, 58: 179–189.
141. PALMER, W. W. Absorption of protein and fat after resection of one-half of the small intestine. Am. J. M. Sc., 1914, 148: 856–866.
142. PARK, ROWELL. Successful removal of 265 cm. of gangrenous intestine. Arch. internat. de Chir., 1904, 1: 106–110.
143. PAUCHET, V. Résection de 4 mètres d'intestin grèle. Gaz. d. hôp., 1905, 78: 1667. Abstracted in Jahresb. f. Chir., 1905, 11: 732.
144. PAYR, ERWIN. Ueber ausgedehnte Darmresectionen. Arch. f. klin. Chir., 1902, 67: 181–201.
145. PECK. Quoted by Harris and Nigrisoli, loc. cit.
146. PECURARIU, OVIDIU. Mesenterialthrombose in 2 Faellen. Clujul med., 1933, 14: 412–418. Abstracted in Zentralorgan f. d. ges. Chir., 1933, 65: 100.
147. PETERSON. Rusch-haupt, Inaugural Dissertation, Bonn, 1901. Quoted from Soyesima, loc. cit.
148. PIDCOCK, BERTRAM H. Two cases of intestinal obstruction. Brit. M. J., 1924, 1: 369–370.
149. POKOTILO, V. L. A case of extensive resection of the small intestine in strangulated hernia. Khirurgiya, 1909, 25: 169–173. Abstracted by W. F. Prior & Co.
150. PÓLYA. Ueber mesenterialsarkome. Budapesti orv. ujság., 1907, No. 30. Abstracted in Zentralbl. f. Chir., 1908, 35: 247.
151. PÓLYA, EUGEN. Die Pathogenese der retrograden Inkarzeration des Darmes. Deutsche Ztschr. f. Chir., 1911, 111: 424–509.
152. PRIBRAM, B. O. Beitrag zur Kenntnis der retrocoecalen Hernien. Mitteilung eines Faelles von Hernia retrocoecalis incarcerata. Resektion von 235 cm. Dunndarm. Heilung. Deutsche Ztschr. f. Chir., 1920, 153: 75–85.
153. PUPOVAC. Wien. klin. Wchnschr., 1920, No. 15, 327. Schmid, loc. cit.
154. REDER, FRANCIS. Personal communication to Cannaday; mesenteric thrombosis. Discussion. Tr. South. Surg. Ass., 1923, 35: 237.
155. RICHTER, JULIUS. Zur Klinik der Uterusperforation. Zentralbl. f. Gynaek., 1917, 41: 41–48.
156. RIVA, ROCCI. See Fantino.
157. ROEMER, G. Ueber ausgedehnte Duenndarmresektion. Deutsche med. Wchnschr., 1918, 44: 1176.
158. ROTHE, HERMANN. Beitrag zur Statistik der incarcerierten Hernien. Beitr. z. klin. Chir., 1902, 33: 140–188.
159. RUGGI. Storia relativa ad un fanciullo di anno 8 al quale furono asportati con successo metri 3.30 d'intestino tenue. Policlin., 1896, 3 (c): 49–62.
160. RYTI, ELSA. Darmresektion und perniziose Anamie Duodecim, 1927, 43: 81–87. Abstracted in Zentralorgan f. d. ges. Chir., 1927, 40: 843.
161. RYTKÖLÄ, T. Tvenne fall av tunntarmsknutar. Finska läk-sällsk. handl., 1924, 66: 627–635.
162. SALTIN, GUNNAR. Tre fall af tarmknut. Finska läk-sällsk. handl., 1912, 54: 292–297.
163. SARNOFF, JACOB. Extensive resection of small intestine: report of recovery after resection of 15 feet of small intestine and hysterectomy. Ann. Surg., 1923, 78: 745–750.
164. SCHILLING, F. Limits of resection of small intestine. Arch. f. Verdauungskr., 1921, 29: 52–58. Abstracted in J. Am. M. Ass., 1922, 78: 854.
165. SCHLATTER, CARL. Ueber die Verdauung nach einer Duenndarmresection von ca. 2 Meter Laenge. Cor.-Bl. f. schweiz. Aerzte., Basel, 1899, 29: 417–424.
166. Idem. Ueber die Darmfunktion nach ausgedehnten Duenndarmresektionen. Beitr. z. klin. Chir., 1906, 49: 1–25.
167. SCHLEINZER, J. Demonstration eines 19 jaehrigen Patienten, bei dem ueber 4 m. Dunndarm reseziert wurden. Wien. klin. Wchnschr., 1917, 30: 772.
168. SCHMID. Gynækol. Kongress 122, Innsbruck. Quoted from Mueller, loc. cit.
169. SCHMID, HANS. Ueber retroperitoneale und mesenteriale Tumoren. Arch. f. Gynaek., 1923, 118: 490–559.
170. SCHNITZLER. Ausgedehnter Duenndarmresektion. Wien. klin. Wchnschr., 1926, 39: 59.
171. SCHUGT, P. Ein Fall von Uterusperforation mit schwerer Verletzung und nachfolgender ausgedehnter Resektion des Duenndarms. Zentralbl. f. Gynaek., 1925, 49: 814–817.
172. SCHUMM, O., and PAPENDIECK, A. Fett und Eiweiss ausnutzung nach umfangreicher Duenndarmresektion. Ztschr. f. physiol. Chem., 1923, 131: 54–59.

173. SENN, NICHOLAS. An experimental contribution to intestinal surgery with special reference to the treatment of intestinal obstruction. Ann. Surg., 1888, 7: 99–115.

174. SHEPHERD, FRANCIS J. Successful removal of an enormous mesenteric tumor and nearly 8 feet of intestine. Brit. M. J., 1897, 2: 966–968.

175. SHIMA, K. Allgemeine Stoffwechseluntersuchungen nach totaler Magenextirpation und ausgedehnter Darmresektion. Beitr. z. klin. Chir., 1931, 153: 275–299.

176. SIEBERT. Inaugural Dissertation, Koenigsberg. Cited from E. Polya, loc. cit.

177. SIMON, R. Triple déchirure traumatique du mésentère; résection de 2m 10 de jejuno-iléon; guérison. Gaz. méd. de Strasb., 1923, 81: 661–662; Personal communication.

178. SINCLAIR, N. F. Remarks on extensive resection of small intestine with notes on a case. West Lond. M. J., Lond., 1924, 29: 24–29.

179. S ÖVALL, S. Ueber Embolieder Arteria mesenterica superior mit Anschluss eines Erfol operierten Falles. Acta chirurg. scand., 1927, 61: 577–586.

180. SMIDT, HANS. Ausgedehnte Darmresektion bei arteriell-embolischem Darminfarkt. Deutsche Ztschr. f. Chir., 1919, 150: 399–408.

181. SMITH, WILBURN. Superior mesenteric thrombosis. Southwest. Med., 1928, 12: 549–555. Fowler, loc. cit.

182. SOHN, ADOLF. Ausgedehnter Duenndarmresektionen. Deutsche Ztschr. f. Chir., 1923, 181: 403–412. Abstracted in J. Am. M. Ass., 1923, 81: 1914.

183. Idem. Zur Frage der Dauerheilung nach ausgedehnten Duenndarmresektionen. Deutsche Ztschr. f. Chir., 1927, 201: 263–265.

184. SOYESIMA, Y. Experimentelle und literarische Studien ueber die ausgedehnten Duenndarmresektionen. Deutsche Ztschr. f. Chir., 1911, 112: 424–466.

185. SPASSOKUKOZKAJA, N. J. Ein Fall von ausgedehnter Duenndarmresektion. Centralbl. f. Chir., 1906, 33: 687.

186. STAEHLIN, E. Resection of 10 feet 2 inches of small intestine with recovery. Ann. Surg., 1907, 45: 49.

187. STASSOFF, B. Experimentelle Untersuchungen ueber die kompensatorischen Vorgaenge bei Darmresektionen. Beitr. z. klin. Chir., 1914, 89: 527–586.

188. STOLZ. Ausgedehnte Darmresektion wegen Gangraen Deutsche med. Wchnschr., 1909, 35: 744.

189. Idem. Spaetresultat einer ausgedehnten Duenndarmresektion. Berl. klin. Wchnschr., 1910, 47: 1685; Muenchen. med. Wchnschr., 1910, 57: 1716.

190. STORP. Ueber die Zulaessigkeit ausgedehnter Duenndarmresektionen. Deutsche Ztschr. f. Chir., 1907, 87: 313–329.

191. STUCKEY, LEO. Zur Kenntnis der retrograden Inkarzeration. Deutsche Ztschr. f. Chir., 1910, 105: 545.

192. SYRING. Coecum-Duenndarm-Volvulus in eingeklemmter Hernie. Beitr. z. klin. Chir., 1913, 82: 695–701.

193. TANTZSCHER. Quoted by Ghedini from Nigrisoli's series, loc. cit.

194. THON. Ueber Knotenbildung des Duenndarms. Deutsche med. Wchnschr., 1909, 35: 742.

195. TOIDA, R. Ueber ausgedehnte Resektion des Duenndarmes und zugleich ein Beitrag zur Stoffwechseluntersuchung des betreffenden Falles. Mitt. a. d. med. Fak. d. k. Univ. Kyushu Fukuoka, 1917, 3: 373–390.

196. TOOMBS, P. W. Resection of intestine following gunshot wound of abdomen. Railway Surg. J., 1914, 21: 98–102.

197. TREVES, FREDERICK. The anatomy of the intestinal canal and peritoneum in man. Brit. M. J., 1885, 1: 415–419.

198. TROTTER, L. B. C. Embolism and thrombosis of the mesenteric vessels. Cambridge University Press, 1913.

199. TRZEBICKY, RUDOLF. Ueber die Grenzen der Zulaessigkeit der Duenndarmresektion. Arch. f. klin. Chir., 1894, 48: 56–92.

200. TUOMIKOSKI, VILJO. Zur Kenntnis der Ausnutzung der Nahrung nach Darmverkuerzungen Skandin. Arch. f. Physiol., 1928, 54: 249–320.

201. TURCK, RAYMOND C. Intestinal resection: successful removal of more than 12 feet of bowel with observations on the subsequent metabolism. New York M. J., 1914, 99: 316–319.

202. VAN VERTS, M. J. Exclusion de la plus grande partie de l'intestin pour un anus contre nature. Bull. et mém. Soc. nat. de Chir., 1903, 29: 610–619.

203. WALLACE, CUTHBERT. A tabular statement of five hundred abdominal gunshot injuries. J. Roy. Army Med. Corps, 1916, 26: 802–806.

204. War Department. The Medical Department of the United States Army in the World War. War Department, 1927, vol. 2, Surgery, Part 1.

205. WATSON, P. Case of extensive resection of small intestine with clinical study of recorded cases. Edinburgh M. J., 1923, 30: 174–184.

206. WEIR, P. F. Sarcoma of mesentery; its extirpation with 8¼ feet of small intestine; peritonitis; death. Med. Rec., 1900, 57: 1137–1138.

207. WERELIUS, A. Successful resection of 12 feet and 2 inches of the ileum in case of criminal abortion. J. Am. M. Ass., 1907, 48: 945.

208. WHITALL, J. DAWSON. Extensive removals of intestine. Report of a case of recovery after resection of 10 feet 8 inches of the ileum. Ann. Surg., 1911, 54: 669–672.

209. WILDEGANS, H. Disturbances of metabolism after extensive resections of small intestine. Deutsche med. Wchnschr., 1925, 51: 1558–1561. Abstracted in J. Am. M. Ass., 1925, 85: 1436.

210. WOHLGEMUTH, KURT. Ueber Tetanus nach Operationen (Gleichzeitig ein Beitrag zur Kasuistik der angeborenen Mesenterialluecken und der ausgedehnten Duenndarmresektionen). Arch. f. klin. Chir., 1923, 123: 409–414.

211. WOOD, W. Q. Case of extensive resection of the small intestine. Edinburgh M. J., 1920, n.s. 25: 61–62.

212. WULSTEN, J. Heilung einer Thrombose der Vena mesenterica superior durch Resektion des gesamten Duenndarmes. Zentralbl. f. Chir., 1929, 56: 3155–3159.

213. ZUSCH. Stoffwechsel nach ausgedehnter Duenndarmresektion. Deutsche med. Wchnschr., 1909, 35: 739

EDITORIALS

SURGERY, GYNECOLOGY AND OBSTETRICS

ALLEN B. KANAVEL, M.D.....Editor
LOYAL DAVIS, M.D.....Associate Editor

DONALD C. BALFOUR, M.D. ....Associate, Editorial Staff

NOVEMBER, 1935

THE TREATMENT OF MALIGNANT TUMORS OF THE UPPER JAW AND ANTRUM: FIFTEEN YEARS OF PROGRESS

IN the treatment of malignant tumors, concerted effort by a group of workers treating a large number of patients in a limited field may obtain results that seem almost unbelievable. This point is well illustrated in a monograph by L. George Ohngren, *Malignant Tumors of the Maxillo-Ethmoid Region*, in which was reported the work of Gunnar Holmgren's service at the Sabbatsberg Clinic, Stockholm. A complete review of the foreign and American literature has been made and those workers credited who have participated in the development of the method of treatment.

Ohngren traced the development of the treatment of these tumors. At first, resection of the jaw was employed; the operative mortality was considerable and few patients remained free of the disease. He then traced the changes that have produced the improved results. The handling of these cases was placed under the direction of those interested in the special field rather than the general surgeons who took care of them previously. At first, pure surgical treatment was employed as a routine method, and the results were poor; then roentgen rays and radium were used in conjunction with surgical treatment, but still the results were not much better. The use of soldering irons or "ferrum candens" was then employed, and this was followed by the employment of large electrocauteries. Finally, in 1922, electrosurgery was used, and in 1927, radium was employed in addition to electrosurgery. In this way much has been accomplished in the care of this group of tumors as compared to the comparatively poor results from surgical treatment alone.

Ohngren, in studying tumors of the upper jaw and antrum, has used an original classification and included three factors: (1) the more or less favorable position of the tumor, (2) the greater or lesser degree of histological malignancy, and (3) the presence or absence of metastasis. In charting the more or less favorable position of the tumor, which of course is a large factor in its curability, he uses a plane which passes from the inner canthus in a direction backward and downward to the angles of the mandible. In this way he has a superior posterior group and an inferior anterior group. It is readily seen that the inferior anterior group of tumors are much more easily accessible to removal, and may get to be of large size without invading areas that make their removal impossible, than the superior posterior group. Each of these groups Ohngren again divides into a lateral and medial group, thus making four groups in all.

The difficulty in gaining access to the medial superior posterior group makes the outlook for them poorest of all, regardless of the type

of malignant tumor. In reviewing the results in 149 cases in which operation was performed, Ohngren classifies them as to position in determining the so called cures. Histological studies have been made in all cases, and in a very thorough manner he has reviewed the results as related to the particular type of tumor present. As would be expected, if recurrence is going to take place, it usually occurs in the first year after operation. In this series there were more than four times as many recurrences in the first year as later. The fact that it was possible to follow all of these cases makes the report very valuable.

The striking improvement in treatment of these tumors over what it was 15 years ago may be appreciated when it is noted that 38.5 per cent of 5 year cures of malignant tumors in this region are reported in this monograph. One must remember, too, that in many of the earlier cases patients were treated during the transitional period, when the technique had not been perfected, so similar patients treated today would probably be handled better.

Future reports of this work should be still better. It is by such work as this that advances are made in our efforts to control malignant diseases. GORDON B. NEW.

CONTROLLING GAS PAINS

EVERY intra-abdominal operation offers the opportunity of a potential ileus, meaning "obstruction of the bowel attended with severe colicky pain" (Stedman). Short of an actual obstruction, either dynamic or adynamic, the normal peristaltic action of the intestines is usually inhibited the first few hours following operation, but early on the second day, intestinal activity is increased, producing what is generally referred to as "gas pains." These occur in greater or less degree even in the simplest operations within the abdomen. They are never regarded seriously unless they persist and result in over distention with continued pain or, as a further phase, a paralytic ileus with decreasing pains. Such conditions present evidence of abnormal complications and are to be dealt with according to indications as outlined in the work of recent investigators.

We are not concerned here with the management of intestinal obstruction. We are interested in methods of controlling the ordinary "gas pains" associated with the average abdominal operation. Since they are due to overactivity of the natural peristalsis of the bowel and since the suppression of the normal intestinal movements would be unwise, it is better to control the pains than to stop them entirely.

In the usual case there is no distention, merely the corkscrew cramps running about at intervals over the abdomen, after the general bodily discomfort and the incisional pain have somewhat abated. The suffering may be acute even when the abdomen is perfectly flat, free from any accumulation of gas. The only justification for the term "gas pains," is that an overacting peristalsis is hastening to get rid of whatever the intestinal canal contains and the patient feels relieved when gas is passed through the rectum. The more purging before operation, the more severe the pains after operation. The solar plexus resents the insult and proceeds to take its revenge. An enema at least 12 hours ahead is the best pre-operative resource and it is well known that emergency operations admitting of no preparation are followed by less pain than formal procedures with elaborate preparation. All this seems to signify that stirring up the intestines beforehand and rendering the bowel too empty will cause the greatest hyperperistalsis after operative interference.

Our object, then, is to encourage the normal peristaltic movement after abdominal

operations; to regulate it, if feasible, not to hinder it. About 20 years ago my associates and myself devised a plan, followed more or less routinely ever since, to be used in every case when annoying peristaltic pain appears.

Of primary importance is the necessity of instructing nurses to recognize the "gas pains" in their very beginning, their fleeting character, their constant change of location, their association with waves of nausea. Success in their management depends chiefly on anticipating their development. The orders are: a mustard plaster, or hot camphor stupes, on the epigastrium; insertion of the rectal tube for 30 minutes; flushing the lower colon through the tube, in and out, with warm saline solution; in a half hour the tube is removed and 10 grains of quinine muriate in 8 ounces of water are injected slowly into the rectum; this is repeated in 4 hours. Generally relief is prompt, but if not complete, the same process is carried out again 6 hours afterward. No other measures are allowed to interfere with these orders, no fussing around to do this or that, until the results of the routine procedure are determined. If gaseous distention ensues, and the pain diminishes, 1/40 grain of eserine salicylate and 1/60 grain of strychnine sulphate are given hypodermically every 3 hours for 3 doses, followed by an alum enema (1 ounce to the quart of warm water) 1 hour after the last dose; on the contrary, if the pain increases with little or no distention, 1/100 grain of hyoscine hydrobromate and 1/12 grain of morphine sulphate are given hypodermically, 1 dose, followed by the alum enema 1 hour later. These accessory orders are seldom needed in the ordinary case, for under the three steps first mentioned, flatus is passed, not infrequently small fecal results are obtained and by the end of the second day the patient is comfortable. Persistence of slight pains may be relieved by ½ grain of phenobarbital, given every 4 hours by the mouth, continued for 2 or 3 days longer.

It might be well to consider the rationale of using the quinine injection. In my student days H. C. Wood taught that quinine stimulated the inhibitory center of the spinal cord. That recollection prompted the use of the most soluble salt of quinine for slowing peristaltic action after mechanical means had been employed to stimulate the activity of the lower bowel. Knowing that the older conceptions of the physiological action of many drugs had been superseded by later researches of modern pharmacologists, I recently asked William deB. MacNider, of the University of North Carolina, to express his views upon the action of quinine for the purpose intended. In a personal communication, he replied:

> My feeling is that the quinine muriate could act in a variety of ways on the intestine to cause the passage of accumulations of gas. In the first place, it could act directly on the involuntary muscle tissues of the intestine. In very weak dilutions quinine tends to stimulate this type of tissue. On the other hand, it could influence the passage of gas through the intestine by its action on the central nervous system, either by stimulating the motor nervous mechanism to the intestine which is the vagus nerve, or it might relax the intestine and permit the passage of gas by stimulating the inhibitory nervous mechanism to the intestine which is, of course, furnished by the sympathetic system.

It is hardly necessary, but perhaps excusable, to mention that the most effective way to prevent "gas pains" is to refrain from adding insult to injury inside the abdomen; to handle the parts politely; to avoid evisceration as far as permissible; to get in and get out safely, swiftly and sweetly; to forsake the ponderous pounding of the "abdominal brain"; and to cleave only unto a gentle attention to the lesions at hand. By giving heed to these observances we may bring hundreds of patients through to convalescence without "gas pains," without anodynes, without meddling of any sort. HUBERT A. ROYSTER.

LANDMARKS IN SURGERY

ILIAC COLOSTOMY

R. W. McNEALY, M.D., F.A.C.S., AND MANUEL E. LICHTENSTEIN, M.D., F.A.C.S., CHICAGO, ILLINOIS
From the Department of Surgery, Northwestern University Medical School

THE first record of colostomy in the modern sense is the suggestion by Littré that the operation be performed for obstruction of the rectum. In *Histoire de l'Académie Royale des Sciences* (1710) under the heading: "Diverse Observations Anatomique" (p. 36) Fontenelle, secretary of the Royal Academy of Science, records that in the body of an infant that died 6 days after birth Littré saw the rectum divided into two parts which did not communicate with each other except by several small bands. It appeared that a part of the rectum had not developed in proportion to the rest of the intestinal canal. As a consequence these parts tore loose from the undeveloped portion and became entirely detached except for the few bands which held them together. Later the upper part of the intestine became filled with meconium while the lower part remained empty. One can see what might follow such an anomaly and how the death of the child would be prompt since its excrement could not be evacuated and whatever might be given to accomplish this would tend to aggravate this condition. The report continues:

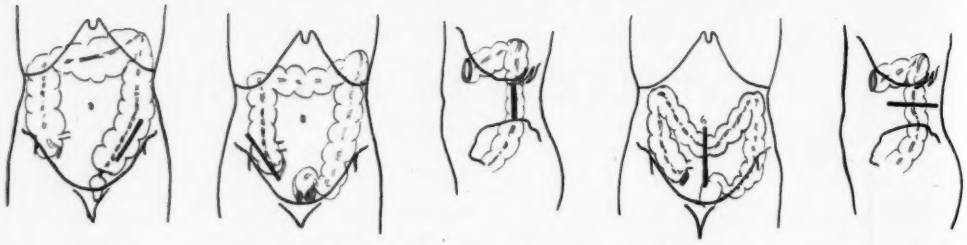
> M. Littré, who wished to make his observation useful imagined and proposed a very delicate surgical operation for cases in which one would recognize a similar conformation. It would be necessary to make an incision into the abdomèn, stitch together the two parts of the intestine after opening them, or at least bring the upper part of the intestine to the abdominal wall where it would never close, and take on the function of an anus. On this simple idea clever surgeons could imagine for themselves the detail which we suppress. It often suffices to know in general that a thing may be possible and not to despair of it at first sight.

In this paragraph there is the suggestion that entero-anastomosis be performed as the operation of choice for sidetracking an obstructive lesion in the bowel. If this is not possible, he suggests as a last resort, that a permanent colostomy be established. There is no record that Littré himself performed this operation. However, in the subsequent literature on colostomy, the left iliac colostomy has been called the operation of Littré.

Alexis Littré (1658–1725) was one of the gross anatomists who lived in the transition period of the 17th and 18th centuries. As the 17th century was notable for the many anatomical discoveries associated with the names of Bartholinus, Wirsung, Highmore, Glisson, Wharton, Willis, Havers, Cowper, Malpighii, Pacchioni, Meibom, Brunner, DeGraaf, Buck, Stenson, Peyer, and others, so the 18th century was notable for the anatomist-surgeons who stood out prominently for their ability to make use of their knowledge of anatomy in clinical surgery. Hunter, Camper, Scarpa, Petit, Anel, Brasdor, Bichat, Chopart, Heister, Pott, Cooper, and Abernethy are some of these anatomist-surgeons. Littré made a study of the anatomy of the urethra and the urethral glands (glands of Littré, 1700) and described a type of hernia (Littré hernia, 1714). His observations concerning anatomy made with a view of surgical application anticipated the advent of the master surgeons whose backgrounds were to be wholesome knowledge of anatomy.

Historically the record of the first colostomy actually performed in 1776 by Pillore was not available in the literature until 1840. On January 14, 1840, in *Gazette des hôpitaux*, vol. 13, 2nd series No. 2, p. 22, there is published a letter which states in part,

> In all the surgical works which speak of the procedures and methods in use for establishing an artificial anus, after having described the procedure proposed by Littré narrate that Duret (of Lyon) and Pillore (of Rouen) have established with success an artificial anus in the adult. It is in *Mémoires de la Société de Médecine de Paris* that one is able to read the details of the operation of Duret, but one is nowhere able to find the description of the operation of Pillore (of Rouen); also it was in vain that Dupuytren begged me to show him where this had been published. M. Velpeau was not very happy when he asked for the same information from my son, then an interne in his service.
>
> On the 16th of last November, M. Amussat wrote my son a letter in which he asked of him again for this observation. He begged him to let him know if he was able to find out something about the known facts and continues as follows: "Pillore (of Rouen) appears to be the first who had practiced the procedure of Littré. Martin, the younger, in a report which he made to the Society of Medicine of Lyon, 1798, after having narrated the facts of Duret, said, p.189 of the report of the acts of the society: 'Pillore, surgeon of Rouen, disciple and contemporary of Lecat, has carried this out successfully but his incision, made in the right iliac region gave access to the cul-de-sac of the cæcum.'
>
> "Fine, surgeon in chief of the hospital in Geneva, says in a mémoire on artificial anus that he had published in the year 13 (1805) in the Annals of the Medical Society of Montpelier the following:
>
> "'(I have unsuccessfully asked and made request of M. Pillore, the father, very advanced in age, and since his death of his son, a surgeon at Rouen, the information concerning when this operation was done, on the case which required it, on the manner in which it was carried out, and also on what the results have been. I hoped that the observation may be found in the papers of the deceased. It is to be regretted that operative medicine should be deprived of the details of an operation which presents great interest and on which Mr. Martin had only a "hearsay knowledge".)'"
>
> It was thus that on going through the papers of my father I found the observation which I give you.
>
> Roue n, January 5, 1840. H. Pillore père D.M.



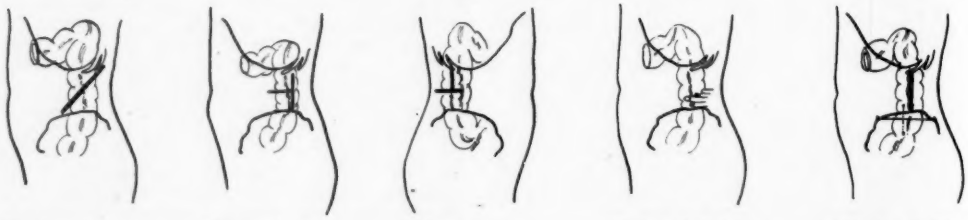
Littré 1710
Dubois 1783

Pillore 1776

Duret 1793
Callisen 1796

Fine 1797

Amussat 1839



Baudens 1842

Keyworth 1848

Phillips 1850

Hodgson's Point

Allingham's Line

Littré suggested left iliac colostomy in 1710. Dubois performed this operation in 1783 but the patient died. Duret in 1793 performed the first successful operation. Pillore suggested and performed the first right iliac colostomy (cecostomy). Duret in 1793 practiced on a cadaver of an infant a lumbar approach to the colon for the purpose of avoiding the peritoneal cavity. The peritoneal cavity was opened and this approach therefore was abandoned. Callisen in 1796 advocated the lumbar approach for intestinal obstruction. Fine in 1797 attempted to relieve an intestinal obstruction by opening the ileum but a low lying transverse colon was opened in the midline below the umbilicus. This was the first recorded median colostomy. The danger of the abdominal approach because of peritonitis was too great in the increasing number of cases of intestinal obstruction that demanded operative relief. Between 1776 and 1839, thirty-three colostomies were recorded and almost all of the patients died. Amussat in 1839 carried out successfully the extraperitoneal approach to the colon in the lumbar region by means of a transverse incision. Baudens in 1842 suggested an incision that was oblique in line with the vessels and nerves. Keyworth and Phillips made T-shaped incisions to facilitate the exposure of the colon. In order that the colon could be properly located, Hodgson described a point and later Allingham in 1870 described a line overlying the colon. This brought the lumbar operation to perfection but the advent of antiseptic and later aseptic surgery resulted in the abandonment of this operation. With the increasing use of colostomy, the approach of Littré became more popular.

Following this appears the case report. It is apparent from this letter that many were interested in the facts regarding this case. It was the first deliberate operation on the colon for relief of obstruction and, contrary to the suggestion of Littré, it was performed in the right lower quadrant of the abdomen. However, there is no evidence that Pillore was familiar with Littré's observation.

Briefly, the patient had been obstructed for 1 month during which time he was unable to evacuate his bowels. He had taken 2 pounds of mercury without any effect on the obstruction. Rectal examination showed a tumor mass that was responsible for the obstruction. As no relief could be obtained by the use of rectal dilators, Pillore proposed that an artificial anus be made. He continues:

> I was then indeed determined to perform the operation but as the case was a very delicate one, I asked five or six of my colleagues to see the patient in consultation with me. No one was of my opinion, but the patient, a man of great sense, present at our consultation, begged them to show him any other means by which he might be saved. They answered that they knew of none. "Very well," he replied, "it is necessary to have recourse to the operation since it alone is able to save me. You agree that it is a fact my disease is mortal."
>
> Encouraged by these very good reasons, I performed the operation in the presence of my confrères, and of six pensioned pupils who were with me then. I chose the cæcum as that part of the bowel most suited to our need, as much by its situation as because it would furnish a reservoir, and by its continual and involuntary action would hasten the evacuation of the intestinal contents. A plate furnished with a sponge in the shape of a button and held by an elastic bandage took the place of a sphincter which could be removed at will when he felt the need, and, by means of a small clyster, he could from time to time cleanse out the reservoir. My patient and I conferred together and thought of all these things before the operation. I then operated.

The operation consisted of exposing the cecum, opening it and suturing its edges to abdominal wall.

The patient improved considerably and his abdomen decreased in size. However, the mercury which had been taken 1 month previously had not been expelled. The patient was put in various positions to facilitate its passage but without avail. After 2 weeks the patient developed pain in the abdomen. On the twentieth day his abdomen became distended

and tender and in spite of emolient fomentations, enemas through the artificial anus and two bleedings, the patient died on the twenty-eighth day.

At autopsy it was found that the cecum was adherent to the edge of the wound except in one angle where there was a small area of suppuration which did not communicate with the peritoneal cavity. The cancerous obstruction which was the primary illness was situated at the rectosigmoid junction and completely occluded the lumen.

The peritoneal cavity was inflamed and adhered to the folds of the intestines. The mercury which the patient had taken was found in one of the loops of the jejunum which it had dragged down by its weight to the hypogastrium behind the bladder. This loop of bowel had several gangrenous areas. All of the mercury was recovered. Pillore continues:

We believe that we could conclude that if the operation has not met our expectations for its success, it was because of the mercury. For it is very probable that when the intestines, which because of their great dilatation had lost their power of action, became empty of stercoral material, peristaltic action was not sufficiently powerful to move the mercury. Then followed inverted and retrograde movements, as announced by the nausea and colic which the patient experienced on the twentieth day of his illness. Considering the pull on the mesentery and intestines by this mass which weighed two pounds, one is not surprised at the gangrenous inflammation which produced the death of the patient.

In 1783, Dubois performed Littré's operation on a three day old infant born with an imperforate anus. The child died on the tenth day. The autopsy showed consolidation of the walls of the rectum which produced obstruction. This case was mentioned by Allen in 1797 in *Recueil de Médecine*, Paris, 3: 123, who stated that he had information that Dubois was the first to practice what Littré had proposed.

The first successful left iliac colostomy (Littré) was performed by Duret in 1793. The case was reported by Duret in *Recueil de Médecine* Paris, 1798, 4: 45. It concerned an infant born with a maldevelopment of the scrotum and perineum. There was an anus but no rectum appeared to be present. A consultation of the physicians and surgeons on the staffs of the various hospitals at Brest was called. After efforts to establish a vent by probing through the site of the anus proved useless this means of therapy was abandoned. About a day and a half after birth a second consultation was held. It was decided to make an artificial anus. In an effort to expose the colon without opening the peritoneal cavity, Duret practiced a lumbar operation on a newborn who had died 15 days after birth. This procedure was not successful as the peritoneal cavity was readily opened. Duret continued:

Those assembled after this trial having prolonged the discussion sufficiently to prove its interest to humanity and honor to surgery, decided: (1) that without extraordinary means the loss of the child was inevitable; (2) that the axiom of Celsus, that, "It is better to employ a doubtful remedy than to abandon the patient to certain death," here found its application; and finally (3) that the decisions of M. Hevin upon laparotomy were not contradicted by this operation since the cause and course of the malady were, as here, recognized. I opened the belly of the little patient in the iliac region in the neighborhood where the sigmoid colon was forming a tumor a little apparent and where the meconium already imparted a deeper color to the skin. I made an opening about an inch and a half long which served for me to introduce the index finger into the belly, with which I lifted and pulled out the sigmoid colon. In the fear that it would immediately fall back into the belly I passed two waxed threads through the mesocolon. I then opened the colon longitudinally. Gas and meconium came out in abundance. When the bowel had emptied itself to a certain extent I applied a dressing. It was simple and was composed of a pierced compress and a body bandage.

The patient recovered from the operation and lived 43 years. Death was reported due to an intercurrent infection.

In 1795, Dagueseau performed Littré's operation for perforation of abdomen with injury to bowel.

In August, 1795, V-, 57, during harvest, occupied in loading his cart with wheat; during an effort to lift a sheaf the band having broken, he lost his equilibrium, fell, and the left side of his abdomen struck one of the stakes forming the side of the cart, with sufficient force to cause it to penetrate deeply. Taken home, M. Daguesceau, a surgeon residing at Chadurec, was called in immediately and decided upon establishing an artificial anus, according to Littré's method. No consecutive accidents occurred; and the patient soon got well and lived 24 years, for he died in 1819, aged 81. A small leather sac was adapted to the opening by Daguesceau to receive the fæces.

The use of the leather colostomy bag was thus established.

Dufresne, who reported the above case in *The Medical Times*, 1840, 10: 446, remarks:

This case, though incomplete, is interesting because at the period at which the operation was performed, only one case had succeeded—that of Duret of Brest in 1795. The patient operated on by (Pillore) in 1776, died 28 days after; that by Antoine Dubois, on the tenth day and that by Desault likewise died.

In 1811, Dagueseau performed Littré's operation for fistula in ano, with a successful result. The details of this case are as follows:

Masset, a potter at St. Eutrope, was affected with several *fistulæ-in-ano* and having consulted Daguesceau, this practitioner considered it impossible to obtain a radical cure, except by establishing an artificial anus in the left hypochondrium, according to Littré's method. This operation, performed in 1811, succeeded; the fistulæ cicatrized; after which the artificial opening gradually diminished in size, and in 2 years was completely closed. The cicatrix, from an excess committed by the patient, burst open, notwithstanding the presence of a truss; but, by appropriate remedies and rest, it healed once more and the man was thus delivered of the two infirmities.

Dufresne who reported this case also in 1840 says:

This case which has no precedent in its favor, may astonish some persons and the operation be considered as not indicated; all that can be said is that Daguesceau's talent was sufficient to enable him to form an opinion as to the absolute necessity of the operation, ere he performed it.

These brief abstracts of case reports and quotations from the literature of a century and more ago demonstrate the ingeniousness of the anatomists and surgeons who conceived and developed this important operation.

THE SURGEON'S LIBRARY

REVIEWS OF NEW BOOKS

THE Woman Asks the Doctor[1] is a remarkably clear and simple "exposition of the special problems in the every day living of women." Its authentic simplicity should counteract much of the pseudo-science that has flooded the market in recent years in response to the very evident desire which women are showing to know more about their physical beings. This desire has long been sensed by the quack and the charlatan; physicians have usually recognized it only when appealed to in individual instances.

It is gratifying to read Dr. Novak's dedication "To woman the Socratic injunction to 'know thyself' has peculiar force and significance. To know or not to know often means the difference between happiness and misery, mental and physical sickness and health, even life and death."

The book is a splendid and rational explanation, toned down to reach the lay mind without "talking down." It presupposes a certain intelligent conception of the fundamentals of life and explains many of the doubts and difficulties that confront the average girl or woman. Especially commendable are the chapters on menstruation, the menopause, and malignancy. The chapter on "Sex" leaves much to be desired. The author states that he has no interest in generalizing on this subject, believing that sex is always an individual problem.

This is a valuable addition to every physician's library, for not only should the physician read this volume, but he should also recommend it heartily to those of his patients who are seeking knowledge.

RALPH A. REIS.

THE fourth edition of the well known Eden and Lockyer *Gynæcology*[2] has been most ably edited by H. Beckwith Whitehouse. A number of new chapters have been added, viz.: the physiology of the female sex organs, gynecological diagnosis, contraception, etc. The chapters on the pathology of the endometrium and on ovarian disease have been completely rewritten.

The last third of this large volume is devoted to surgery. It is most complete, well illustrated, and most inclusive, containing as it does all of the accepted gynecological procedures in use today. The section on gynecological diagnosis and treatment is also most excellent. It contains a splendid differential diagnosis for each condition together with an adequate discussion of the various methods of treatment.

It is most pleasing to read the new chapter which has been added on contraception. It is short but complete, discussing all of the various contraceptive methods and devices. This subject belongs in a modern work on gynecology and it is unfortunate that the vast majority of authors continue to omit the topic completely.

The many illustrations are worthy of comment, especially the many excellent color plates which are found throughout the book. This volume is to be recommended most heartily. It is the most complete one volume work on the subject in the English language and should be found in the library of every physician who is interested in the subject of gynecology.

RALPH A. REIS.

THE twelfth and last edition of Osler's classic[3] was revised and edited by the late Dr. McCrae. The revision has been thorough and complete. The type used is easily readable but allows more words per page thus decreasing the size of the book. The general outline of Osler's original volume has been followed. Mention is made of new thought and procedure, but the text is characteristically conservative. There is very little discussion of theory. The chief alterations have been made in diagnosis and therapy. New conditions are described and diseases which have recently become of particular interest receive special attention. There is practically an entire new discussion on such diseases as undulant fever, chronic hyperinsulinism, digestive disturbances due to food allergy, the anemias, certain phases of heart disease, subarachnoid hemorrhage, and countless others. The section on diabetes mellitus has received particular attention and new food tables are included. This work, always an outstanding textbook, has been brought up to date and should be a valuable addition to every doctor's library.

WILLIAM H. HOLMES.

[1] THE WOMAN ASKS THE DOCTOR. By Emil Novak, M.D., F.A.C.S. Baltimore: Williams & Wilkins Co., 1935.

[2] GYNÆCOLOGY: FOR STUDENTS AND PRACTITIONERS. By T. Watts Eden, M.D., C.M. (Edin.), F.R.C.P. (Lond.), F.R.C.S. (Edin.), F.C.O.G., and Cuthbert Lockyer, M.D., B.S. (Lond.), F.R.C.P. (Lond.), F.R.C.S. (Eng.), F.C.O.G. 4th ed. by H. Beckwith Whitehouse, M.B., M.S. (Lond.), Ch.M. (B'ham.), F.R.C.S. (Eng.), F.C.O.G., F.A.C.S. (Hon.). London: J. & A. Churchill, Ltd., 1935.

[3] THE PRINCIPLES AND PRACTICE OF MEDICINE. By Sir William Osler, Bt., M.D., F.R.S., and Thomas McCrae, M.D. 12th ed. New York and London: D. Appleton-Century Co., 1935.